CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20998/S007

MEDICAL REVIEW(S)

Medical Team Leader Review of Supplemental NDA

CELEBREX™ (celecoxib)
sNDA 21-156
Sponsor: G. D. Searle & Co.
Submission Date: June 25, 1999

On December 31, 1998, Celebrex was granted marketing approval for the relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis. The sponsor has submitted clinical efficacy and safety data in support of the following new indication for Celebrex: reduction in the number of adenomatous colorectal polyps in familial adenomatous polyposis patients. The proposed dose of Celebrex is 400 mg BID. The sponsor has requested consideration for accelerated marketing approval under Subpart H (21 CFR 314.510) based on demonstration of improvement in a surrogate endpoint. The application has been granted a priority review and the user fee date is December 25, 1999.

A single randomized, double-blind, placebo-controlled, study (Study 001) has been submitted. A total of 83 patients received treatment with either placebo, Celebrex 100 mg BID, or Celebrex 400 mg BID for six months (with a 1: 2: 2 randomization). The study population was heterogeneous in that 58 patients had had prior subtotal or total colectomy whereas 25 patients had an intact colon. Thirteen patients had the attenuated form of FAP, a more favorable phenotype.

Comparing baseline demographic characteristics across study arms, a number of imbalances were noted. Compared to placebo patients, patients on the Celebrex 400 mg BID were younger (median age 31 years vs. 40 years on placebo) and were randomized sooner after prior colectomy (median of 9 years vs. 15 years on placebo). In addition, more patients with intact colons received Celebrex 400 mg BID (38% vs. 29% on placebo) and more patients on this arm had attenuated FAP (32% vs. 12% on placebo). Although some of these baseline imbalances could have favored the Celebrex 400 mg BID arm, post-hoc covariate analyses failed to demonstrate an impact of these imbalances on the primary efficacy outcome of the trial.

One area of the rectum, two areas in the duodenum and up to four areas in the colon were identified at baseline and re-evaluated at six months. The primary efficacy endpoint was the mean percent change in colorectal polyp count determined from color still photographs obtained endoscopically at baseline and six months. The secondary endpoint was the mean percent change in duodenal plaque-like polyps at six months. Global assessment of videotapes of the duodenum, colon and rectum served as supportive evidence of efficacy. An expert panel of five reviewers who were blinded with respect to treatment arm and chronologic order reviewed baseline and six-month videotapes.

Efficacy

The mean reduction in colorectal polyp count was 28% on the Celebrex 400 mg BID arm,

15% on the Celebrex 100 mg BID arm and 5% on placebo. Only treatment with Celebrex 400 mg BID was associated with a statistically superior mean reduction in polyp counts, with $p = 0.003$.

FDA, in consultation with Dr. James Lewis of Georgetown University, reviewed the still color photographs of the rectum submitted on 28 patients enrolled at one of the two study sites (St. Mark's Hospital, London). Reviewers were blinded to treatment arm. There was excellent agreement with the applicant's report of mean percent change from baseline in rectal polyp counts for the 13 patients on the Celebrex 400 mg BID arm evaluated (32% reduction per FDA vs. 33% for the applicant). Consistent agreement was not achieved however, when still photographs for 11 patients on Celebrex 100 mg BID and 4 patients on placebo were evaluated.

Global assessment of colonic and rectal videotapes was also analyzed. At the six-month time-point, four of five reviewers assessed rectal videotapes as "better" for six of 29 (21%) patients on Celebrex 400 mg BID. Similarly, four of five reviewers assessed colonic videotapes as "better" for two of 10 (20%) patients on Celebrex 100 mg BID.

The mean reduction in duodenal plaque-like polyp counts was 17% on the Celebrex 400 mg BID arm and 1% on placebo. On the Celebrex 100 mg BID arm, mean polyp counts increased due to the fact that two patients without baseline disease developed polyps in the duodenum on study. Treatment with Celebrex 400 mg BID was not associated with a statistically different mean reduction in polyp counts, with $p = 0.4$. Thus, the beneficial effects observed in the colon and rectum were not predictive of similar effects in the duodenum.

Safety

Celebrex 400 mg BID is well tolerated and its safety profile is similar to that which is labeled for the osteoarthritis and rheumatoid arthritis populations. Of note, 5% (3/58) of patients with FAP who had prior intestinal surgery and who were treated with Celebrex developed worsened ulcers at the anastomotic site, but these were all of mild severity.

ODAC Summary

The Oncologic Drugs Advisory Committee (ODAC) members were sufficiently persuaded that the observed effects in focal areas of the colon and rectum predicted for outcomes in the whole colon and rectum (15 – yes, unanimous). They also agreed that these changes did not predict for outcomes in the whole gastrointestinal tract, including the duodenum (14 – no, 1 – abstention). They believed that the result in this single study was persuasive enough that it be accepted as evidence of a sustained reduction in focal polyps (14 – yes, 1 – abstention).

Regarding the meaningfulness of the finding of colorectal polyp reduction, the majority of ODAC members believed that a reduction of some magnitude was "reasonably likely" to predict clinical benefit in FAP patients (13 – yes, 2 abstentions), and that a mean 28%

reduction was of sufficient magnitude to predict such benefit (12 – yes and 3 – abstentions). Thus, it was concluded that colorectal polyp reduction was a reasonable surrogate endpoint upon which accelerated approval could be based.

Fourteen ODAC members voted in favor of accelerated approval (with 1 abstention). There was general agreement that Celebrex treatment should be labeled as adjunctive therapy to the usual care of FAP patients (e.g., endoscopic surveillance, prophylactic surgery) and that the package insert contain strong warnings emphasizing the need for practitioners to continue to provide usual care to FAP patients despite the addition of Celebrex.

It was also noted that with aggressive surveillance and surgical management, the risk of colorectal cancer in FAP patients has been declining in recent years. Detection and management of duodenal cancer and desmoid tumors in these patients remain challenging problems however. Thus, it was surmised that a substantial departure from the usual care of FAP patients would be unlikely in the foreseeable future despite concurrent use of Celebrex. For patients who refused FAP-related surgery, the availability of Celebrex would be expected to offer some measure of benefit as well.

The optimal duration of Celebrex treatment was not adequately addressed in the controlled FAP trial. When asked whether there was adequate evidence of a persistent effect on colorectal polyps with continued use of the drug, the response was clearly mixed (6 – yes, 6 – no, 3 – abstentions).

Post-Approval Commitments

The study submitted in this supplemental application provided information on colorectal polyp counts after six months of therapy with Celebrex, but evidence of net clinical benefit in FAP patients was not demonstrated. The potential clinical benefits of treatment of FAP patients with a drug such as Celebrex are numerous, including: reduction of gastrointestinal or other FAP-related cancers, reduction in the need or frequency of polypectomies, preservation of the rectal segment (without increasing cancer risk) in patients with subtotal colectomy, and/or delay of prophylactic colectomy (without increasing cancer risk) in adolescents prior to phenotypic expression of the disease. Under Subpart H regulations, post-marketing studies to verify and describe the clinical benefit of Celebrex in patients with FAP would be required.

Searle has agreed to conduct a placebo-controlled randomized trial in adolescents with FAP aged 12 to 19 years who are genotypically positive but phenotypically negative. The primary efficacy endpoint will be prolongation in the time to phenotypic expression of the disease. A 2:1 randomization is proposed with 154 patients receiving Celebrex 400 mg BID and 77 receiving placebo, and will be powered to show a difference of 40% for Celebrex relative to placebo. Patients who develop phenotypic disease will be offered the opportunity to receive open label Celebrex 400 mg BID. The study blind will not be broken. A secondary endpoint – time to initial surgery - will also be assessed.

A long-term registry of clinical outcomes in FAP patients will also be requested as a post-marketing commitment. Searle has proposed enrolling FAP patients aged 12 years or above to a single arm multicenter trial of Celebrex 400 mg BID. Eligible patients would include patients who are genotype and phenotype positive who a) have not had primary prophylactic surgery; b) have had primary prophylactic surgery, but not secondary (additional) surgery; and c) have had both primary and secondary surgery. Usual care (endoscopic monitoring and surgery) will be provided. Time to FAP-related events (FAP-related surgery, duodenal disease, desmoids, cancer and death) and adverse events will be compared to untreated historical controls.

Recommended Regulatory Action

Supplemental NDA 21-156 for CELEBREX™ (celecoxib) is approvable under the Subpart H regulations for the reduction in the number of adenomatous colorectal polyps in familial adenomatous patients, as an adjunct to usual care (e.g., endoscopic surveillance, surgery). Approval is based on a mean 28% reduction in a surrogate endpoint - colorectal polyp counts – observed after six months of therapy with Celebrex 400 mg BID. The videotaped endoscopic appearance of the colon and rectum was improved in approximately 20% of patients on Celebrex 400 mg BID. These findings are supported by a) evidence from animal colon tumor models that demonstrate a reduction in the incidence and multiplicity of tumors with Celebrex exposure, and b) numerous clinical studies, mostly small, uncontrolled series, demonstrating the ability of other NSAIDs, notably sulindac, to reduce colorectal polyps in FAP patients.

Approval is granted with the requirement that the applicant perform a post-marketing study to demonstrate clinical benefit in FAP patients with due diligence. Searle is committed to the conduct of a placebo-controlled randomized trial in adolescents with a genetic diagnosis of FAP. A significant prolongation in time to phenotypic expression for Celebrex relative to placebo in this study could support conversion of the accelerated approval to traditional marketing approval for the FAP indication. In addition, a registry of clinical outcomes in FAP patients will be required. Annual reporting of outcomes in registry patients will be required.

Additional phase 4 commitments that are not a condition of the accelerated approval include the submission of data on patients from the randomized FAP trial (Study 001) regarding polypectomy results, information on dietary habits, and results of biomarker studies.

In a related development effort, Searle has committed to and begun accrual on a study of Celebrex in patients with sporadic adenomatous polyps. This study will randomize approximately 2000 patients over three years to placebo, Celebrex 200 mg BID or Celebrex 400 mg BID. Eligible patients will have had at least one adenomatous polyp removed within three months of study entry. The primary efficacy endpoint is the proportion of patients with new adenomas at year 1 and year 3. This study may provide indirect supportive evidence of efficacy in the FAP population, and serve as the basis for an additional claim in sporadic adenomatous polyps.

/S/ 12/22/99

Julie Beitz, MD Date

cc:
NDA 21-156/ HFD-150 Division File
HFD-150/ J. Chiao
HFD-150/ P. Zimmerman

MEDICAL OFFICER REVIEW OF NDA#21-156

Drug Name: CELEBREX ™ (also known as CELEBREX or Celecoxib or SC-58635)
Applicant: G. D. Searle and Company, 4901 Searle Parkway, Skokie, IL 60077
Date submitted: June 24, 1999
Date received by DODP: June 30, 1999
Date of review: December 22, 1999

Review Team:

Judy H.Chiao, M.D.	Medical Reviewer
Julie Beitz, M.D.	Medical Team Leader
Wendelyn Schmidt , Ph.D.	Pharmacology / Toxicology Reviewer
Paul A. Andrews, Ph.D.	Pharmacology / Toxicology Team Leader
Sung Kwang Kim, Ph.D	Chemistry Reviewer
Rebecca Wood, Ph.D.	Chemistry Team Leader
John Duan, Ph.D.	Clinical Pharmacology / Biopharmaceutics Reviewer
Atiqur Rahman, Ph.D.	Clinical Pharmacology / Biopharmaceutics Team Leader
John Lawrence, Ph.D.	Statistical Reviewer
Gang Chen, Ph.D.	Statistical Team Leader
John Senior, M.D.	Medical Officer, DGCDP
Mark Avigan, M.D.	Medical Officer, DGCDP
James Lewis, M.D.	Special Government Consultant
Gus Turner, Ph.D.	Division of Scientific Investigation
Paul Zimmerman	Project Manager
Dottie Pease	Project Manager Team Leader

1. General Information

Drug Name:	Celebrex™ (CELEBREX or Celecoxib or SC-58635))
Applicant:	G.D. Searle and Company
NDA Submission Date:	June 24, 1999
Pharmacologic Category:	COX-2 inhibitor
Proposed Indication:	Familial Adenomatous Polyposis
45-Day Meeting:	August 18, 1999
FDA Requests for Information:	August 18, 1999
Sponsor's Response:	August 19, 1999
Training session with Dr. Wallace from St. Mark's Hospital	October 8, 1999
FDA request for information on dietary assessment	October 25, 1999
FDA-Searle-NCI Meeting to discuss phase IV trial design	October 25, 1999
Sponsor response to FDA request for dietary assessment	November 10, 1999
Sponsor submitted revised indication	November 12, 1999
FDA request for information	November 17, 1999
FDA request for MD Anderson photographs	November 23, 1999
Teleconference to discuss phase IV trial design	November 29, 1999
Teleconference regarding MD Anderson photographs	December 1, 1999
FDA received MD Anderson photographs	December 3, 1999
Teleconference to discuss phase IV trial design	December 6, 1999
Training session from Dr. Steinbach from MD Anderson	December 9, 1999
ODAC Meeting:	December 14, 1999
FDA request for information	December 15, 1999
Post-ODAC Meeting: Labeling	December 16, 1999
Teleconference to discuss phase IV trial design	December 17, 1999

1.1.Drug name and chemical characteristics

1.1.1. Generic /USAN name

CELEBREX

1.1.2. Trade name

CELEBREX ™

1.1.3. Chemical name :

(4-[5-(4-methylphenyl)-3-trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide)

1.1.4. Structural formula

The empirical formula for CELEBREX is $C_{17}H_{14}F_3N_3O_2S$, and the molecular weight is 381.38.

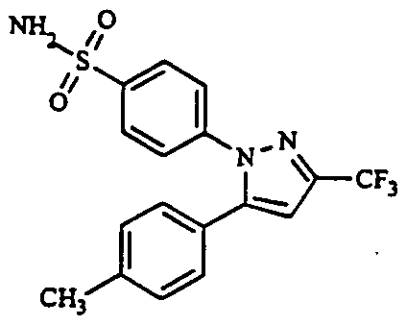

Figure 1. Chemical Structure of CELEBREX™

1.1.5. Formulation

CELEBREX oral capsules contain 100 mg and 200 mg of CELEBREX. The inactive ingredients in CELEBREX capsules are croscarmellose sodium, edible inks, gelatin, lactose monohydrate, magnesium stearate, povidone, sodium lauryl sulfate and titanium dioxide.

1.1.6. Foreign marketing experience

This information is from the Applicant's supplemental NDA volume 1.1 (RA-FAPCELE-15).

CELEBREX was approved on December 31, 1998 by FDA for relief of the signs and symptoms of osteoarthritis or rheumatoid

arthritis in adults (NDA 20-998). In addition, CELEBREX is currently being marketed in Argentina, Brazil, Canada, Mexico, and Switzerland.

1.1.7. Pharmacologic category

Non-steroidal anti-inflammatory drug (NSAID): Diaryl substituted pyrazole

1.1.8. Proposed supplemental indication

CELEBREX is indicated for the regression and prevention of adenomatous colorectal polyps which may lead to the development of colorectal cancer in patients with familial adenomatous polyposis (FAP)

1.1.9. Dosage form(s) and route (s) of administration

The recommended oral dose for FAP patients is 400 mg (2 X 200 mg capsules) twice per day for this supplemental indication

1.1.10. Related drug(s)

Vioxx (Merck): a selective COX-2 inhibitor
Other nonsteroidal anti-inflammatory drugs (NSAIDs)

2. Regulatory History

This part of the review is a summary of the relevant sections in the supplemental NDA as well as correspondence and minutes of meetings between the Applicant and FDA.

CELEBREX is synthesized by Searle and currently marketed for relief of symptoms of osteoarthritis or rheumatoid arthritis under NDA 20-998. The clinical development of this drug in cancer chemoprevention was pursued under IND in collaboration with the Chemoprevention Branch of the National Cancer Institute (NCI/DCP). Under the above IND, CELEBREX was studied in FAP patients and is currently being studied in patients with hereditary non-polyposis colorectal cancer (HNPCC). NCI has authorized Searle to use results from the FAP trial (Study 001) to support this supplemental NDA.

November 13, 1996: NCI submitted IND which contained a

protocol of a randomized, double-blind, placebo-controlled phase II trial of CELEBREX in patients with FAP

February 26, 1998: Meeting between DODP, NCI and G.D. Searle Pharmaceuticals, Inc. to discuss trial design and development plans. The following agreements were reached:

- Determination of efficacy will be based on human clinical data.
- Regarding the validation of biomarkers, human data is fundamental to demonstrate utility of biomarkers. At this point in time, biomarkers are neither necessary nor sufficient for approval.
- FDA considers adenomatous polyps to be neoplastic lesions that may progress to colon cancer and are amenable to a chemopreventive intervention.
- Depending on the results from clinical trials, a chemopreventive intervention may be identified that prevents or resolves adenomatous colon polyps. ***Patients receiving the chemopreventive intervention should be followed to assess the incidence of colon cancer in the treated population. It may be possible to demonstrate alternative clinical benefits, such as a reduced need for surgeries or increased retention of the rectal segment.***
- FDA agrees that it may be possible to file an NDA based on effects on adenomatous polyps as a surrogate endpoint. ***A clinically significant reduction in the number of polyps is helpful but may not be sufficient because the overall results in the entire colorectal remnant need to be consistent. Study 001 is exploratory in nature (heterogeneous population, endpoints of uncertain clinical significance). Once this trial is completed, a multicenter trial will be needed, based on a well-defined patient population and evaluation of results using clinically relevant endpoints. A process needs to be defined whereby adequate numbers of patients are enrolled on study so that results for a duration of use in excess of 6 months can be obtained.*** The company replied that they can provide additional data that may be reassuring regarding the study population (e.g. study probably includes ***few if any patients with the attenuated form of FAP***, and ***relatively few patients who have not had surgery*** have been enrolled).
- The results from Trial 001 may support the proposed indication ("CELEBREX is indicated for the regression and prevention of colorectal adenomatous polyps which may lead to the development of colon cancer in patients with FAP"). However, a second study may be needed for approval. The exact indication will follow review of the data. ***A plan is needed for long term follow-up of the patient population in trial 001, with attention to data collection***

concerning the incidence of colorectal carcinoma, and the occurrence of further ablative therapy.

- Comments on Study 003: Modulation of COX-2 expression in HNPCC carriers/patients (Study 003) is inadequate for accelerated approval of CELEBREX for the prevention of adenomatous polyps.
- Comments on study 005 (sporadic adenomatous polyps i.e. SAP): As a polyp prevention endpoint, the prevention of subsequent polyps in patients with a cleared colon is acceptable. Based on the literature descriptions (e.g., those describing the Polyp Prevention Trial, PPT, and the Colorectal Adenoma Prevention Trial, CAPS), the period of follow-up may need to be longer than 12 months or the sample sized larger to show a difference in polyp incidence. Whether or not patients are treated with study medication for more than one year, consideration should be given to a follow-up period that extends beyond one year, consistent with standard practice for monitoring after the diagnosis of a sporadic polyp. A protocol should be submitted, which among other information provides the rationale for an endpoint chosen to demonstrate clinically significant polyp reduction.
  - FDA needs to review the protocol for Study 005; but it is possible that a one-year study with positive results could be adequate for an NDA filing. Longer term data will be of interest and will probably be required.
  - Approval for a SAP indication will rely mainly on the results from Study 005
  - Studies of , and labeling for regression in SAP are problematic
  - Depending on the results, data from a FAP study (001) may support an indication in SAP.
  - For the present, proposed indications should be specific to the patient population that has provided the pivotal clinical data
- Comments on Study 007 (SAP): The endpoint is not acceptable for approval. The regression of a single, small, sporadic, unbiopsied, polypoid lesion in the colon is inadequate for use as clinical evidence of a CELEBREX effect. Please submit a protocol for Study 007 which describes how this study will protect the patients studied, considering the departure from standard practice that it represents.
- Comments on whether accelerated approval of new drugs for serious life threatening illness applies to regression and prevention of adenomatous polyps which may lead to the development of colon cancer:
  - A demonstration of the prevention (or possibly the delay in progression) of adenomatous colorectal polyps is potentially acceptable for accelerated approval for FAP.

- *For conversion to regular approval, reduction in the incidence of colorectal cancer or other clinical benefits would be considered. If clinical benefits can be demonstrated with follow-up of the first study (001) then it may be possible to fulfill the requirements for conversion to full approval, otherwise a second study will be necessary to demonstrate other potential benefits that might allow conversion to full approval.*
  - "Making the case" cannot be based only on epidemiology; it must be based on data from these (FAP) patients.
  - SAP patients may possibly be used to support a FAP indication
  - Regarding accelerated approval for SAP, this must be based on follow-up data
- Other FDA comments: An NDA for the use of CELEBREX in the treatment of FAP could be filed in advance of an NDA for another potential CELEBREX indication. Safety data from clinical trials for indications other than polyp prevention/regression might be pertinent, especially for a duration of use of 6 months or longer.

November 23 1998: Teleconference between DODP, NCI and Searle to obtain agreement on the suitability of the revised FAP trial statistical plan and obtain agreement that the FAP trial is considered a pivotal study in support of the proposed FAP revised claims of 1) prevention of colorectal adenomatous polyps which may lead to the development of colon cancer and 2) regression and prevention of colorectal adenomatous polyps which may lead to the development of colon cancer in patients with FAP and/or 3) regression and prevention of duodenal adenomatous polyps which may lead to the development of duodenal cancer in FAP patients.

- Searle added a co-primary endpoint, i.e., change in the duodenal disease. The sponsor explained that the high percentage (58%) of duodenal polyps in these patients is an opportunity to assess effects of the drug. In addition, the sponsor provided a reference (Wallace, M. et al: British Journal of Surgery. 85: 742-750, 1998) to support the statement that upper GI (duodenal) cancer has overtaken large bowel cancer as a leading cause of death in FAP patients.
- Searle added a duodenal ampulla analysis in the statistical analysis plan and stated that a large proportion of patients had enlargement of the ampulla at baseline and abnormalities in this area are common and important.
- The follow-up period after the last dose on therapy has been shortened. The sponsor stated that this change enlarges the window for the follow-up phone call only (post 6 month endoscopy phone call)
- The statistical analysis plan was changed from comparing all three arms to comparing only the high dose to placebo in the primary

analysis. The sponsor stated that they expected to see efficacy in the high dose arm and therefore did not want to compare high dose vs. low dose. The sponsor reassured DODP that the study blind has not been broken because of toxicity, etc. The database would be frozen on December 4, 1998 and the blind would be broken on December 8, 1998. DODP had the following statistical comments:

- The sponsor will need to adjust for multiple endpoints and for multiple comparisons between arms
- We are always concerned when there are changes in endpoints of analyses this late in a study. Has the blind been broken or the treatments unblinded because of toxicity, etc?
- If addition of a co-primary endpoint was based on the data analyzed, results of such analysis should be considered as exploratory and a confirmatory study is necessary.
- ITT should include all patients as randomized.
- The proposed plan for exclusion of missing data may not be appropriate
- If any conclusion will be made based on secondary endpoints, the significance level should be adjusted for the number of secondary endpoints.

December 8, 1998: A teleconference was held between DODP, NCI and Searle to discuss the December 7, 1998 revised FAP trial statistical plan:

NCI/DCP and Searle provided the following changes in the statistical plan

- There will be one primary endpoint: percent change from baseline for colorectal polyps. The key statistical treatment comparisons will be high-dose vs. placebo and low-dose vs. placebo with each comparison at type I error of 0.05.
- There will be one secondary endpoint: percent change in area of duodenal plaque-like polyps. The key statistical treatment comparisons will be high-dose vs. placebo and low-dose vs. placebo with each comparison at type I error of 0.05. No conclusions will be based on the endpoint unless the primary endpoint attains statistical significance.
- All other variables listed in the August 18, 1998 version of the analysis plan will be tertiary variables.
- The Intent-to-treat analysis will include all randomized patients.
- Missing data will be handled as follows:
  -relative to the primary endpoint, there are **five discontinued patients with no data beyond baseline. For these five, all % changes from baseline scores for the primary endpoint will be defined as 0%.** This will ensure that all five will be included in the intent-to-treat analysis per the Agency's recommendation Nov 23.

-relative to the secondary endpoint, there are two patients with no duodenal plaque at baseline and some duodenal plaque at end of study. Since the % change from baseline for these patients can't be determined, the baseline value will be defined as 1 % for both these patients. This will result in both being included in the secondary endpoint analysis.

Concerning item 1 above the FDA stated since two comparisons (high dose vs. placebo and low dose vs. placebo) will be performed and the conclusion may be only based on results of one of the two comparisons, if 0.05 is used as the significance level for each comparison, the overall type I error will be inflated. FDA always requires adjustment for such multiple comparisons. However, the sponsor may allocate the α in an unequal manner, i.e., assign more α to one comparison which the sponsor believes more important (e.g., 0.04 and 0.01). The total α level should be controlled at the 0.05 level.

The sponsor noted that they would apply 0.04 to the high dose and 0.01 to the low dose comparisons.

Concerning item 2 above the FDA stated that it is acceptable to use "percentage change in area of duodenal plaque-like polyps" as a secondary endpoint. However, the α level should also be adjusted for the two comparisons (see comment 1).

Concerning item 3 above the FDA stated that the sponsor needs to clarify whether any claims will be made based on those tertiary variables. Usually, the efficacy conclusion will be based on evaluation of the primary endpoint and results of secondary endpoint analyses will be considered for labeling. Those tertiary variables the sponsor wishes to consider including in labeling in the future should be treated as secondary endpoints and adjustment for multiple endpoints is necessary.

The sponsor noted that they intend to make no claims on the tertiary endpoints.

Concerning item 4 above the FDA stated that the ITT analysis plan is acceptable.

Concerning item 5 above the FDA stated that the plan for missing data is acceptable.

Regarding the pivotal status of this study, the FDA stated that it is acceptable to submit this single study for NDA filing.

December 11, 1998: FDA response to the sponsor's revised amendment to the statistical analysis plan (Serial number 021 dated 12/9/9*):

- The sponsor's revised amendment to the statistical analysis plan for study IQ4-96-02-001 submitted on December 9, 1998 is acceptable to FDA.
- Regarding the tertiary variables, both the sponsor and the FDA agree that no conclusions or labeling claims will be made based on the results of analyses of tertiary variables.
- A supplemental NDA would be acceptable for filing based on this single trial in FAP. Safety data in FAP patients should be compared to available safety data in arthritis patients. The details of the format and content of the NDA should be discussed at a pre-NDA meeting prior to filing.

March 29, 1999: Meeting between DODP, NCI/DCP and Searle to discuss the format of the application. The current plan appears acceptable to DODP, except for the following:

- PK data should be submitted for review.
- Individual patient data listings will need to be provided, and the methodology for obtaining and independently confirming these data must be clearly presented in the application.
- The data regarding interval development of new polyps, the number of polyps that were removed/biopsied on study and the presence of areas of confluence should be presented.
- We will need to verify your polyp counts and all other endpoints. Please submit your finalized methodology for performing your assessment including counts and measurements. Please submit photos, videos, and case report forms on all patients.
- You should consider how to analyze the adverse experience to account for the difference in treatment duration between polyp patients and arthritis patients.
- Additional analyses of interest may become evident as the review progresses. Will the primary data be made available electronically to facilitate the review process? The preferred format is SAS transport files. An annotated case report form is requested with the submission of the electronic data set.

The sponsor noted that it would provide both PC SAS data sets and SAS transport files. Both annotated CRFs and processed data set will be provided.

Additional FDA comments:
Based on this package, an sNDA would be acceptable for filing however, the following concerns should be addressed in the sNDA:

- Sample size
- ***Lack of clarity in defining and assessing endpoints***
- ***Short treatment duration***
- Dose finding is limited
- No data for long term dosing at the proposed dose
- ***Adequacy of polyp reduction as a surrogate endpoint for clinical benefit, e.g., reduction of the risk of colon cancer, reduction in the need for colectomy, etc.***
- The proposed package insert should reflect the data, i.e., the reduction in the number of existing polyps compared to placebo. ***The data do not appear to support a claim for prevention of polyps much less cancer.***
- Assuming this is recommended for approval, what are your plans for your post-marketing study to confirm clinical benefit in FAP?
- Do you have plans for evaluating safety and efficacy beyond 6 months?

April 26, 1999: Teleconference between DODP and Searle: The purpose of this impromptu telecon was to clarify and discuss the sponsor's proposal for submission of video tapes, photographs, and CRFs regarding the NDA for FAP. Discussion:

- The sponsor proposed to submit 4 to 6 videocassettes per patient (83 patients) for FDA review. They would be packaged about 20 videos per box in about 15 to 20 boxes. The Division noted that the duodenal videos were not being requested at this time and that only the videos used to obtain the sponsor's primary endpoint (colorectal polyp counts) results should be submitted. The videos must be provided in NDA jackets and only one copy need be submitted. The sponsor noted that only one or two videos would fit into one NDA jacket. Ms. Piergiovanni proposed to contact the sponsor's medical personnel to identify which videos were used to obtain their results and to advise the Division of her findings. Ms. Piergiovanni also suggested that the Agency and sponsor could meet to review the sponsor's method of assessment if this would be helpful.
- The sponsor noted that they plan to submit super VHS copies of the original videos and that digital reproduction had not been possible for the videos produced in the UK. The Division noted that the copies need to be of sufficient quality for the Agency to duplicate the sponsor's results. Lesser quality copies may be disadvantageous to the sponsor if the Agency is unable to duplicate their efficacy results.

- The sponsor proposed to submit sleeved photographs tabbed per patient in NDA jackets. The Division proposed that the sponsor consider providing the photographs digitally. If the sponsor chose to pursue the digital format, the Division suggested that they first provide examples of the photographs and digital reproductions of those photographs for the Division to evaluate, to assure that they are of comparable quality for review.
- The proposal for submission of CRFs on CD-ROM (consistent with FDA requirements) is acceptable.

June 24, 1999: NDA 21-156 was submitted. Searle also submitted a Review Aid which contained the following:

- SAS transport files, PC SAS data sets, the processed dataset as well as hard copes of annotated CRFs of clinical data for FAP study 001
- A manual on how assessments (polyp counts, size measurements etc) were made
- ASCII files containing the NM-TRAN/PREDPP data set (containing individual plasma concentration data for FAP clinical study 001) and NM-TRAN commend file used in the population PK data analysis
- Electronic Case Report Forms on CD-ROM
- A CD-ROM containing the proposed text for labeling , a PDF rendition displaying the volume and page annotations, the Section 3 Clinical Data Summary (Report 804), the Comparison of Safety Data between the FAP and Arthritis Populations (Report 811), and the FAP Clinical Study (Report 001)

July 8, 1999: DODP determined that this application will be reviewed under 21 CFR 314 Subpart H for accelerated approval.

August 18, 1999 (Day 45 meeting): FDA request for information sent to Searle:

- We have conducted a preliminary review of your supplemented NDA 21-156 for filing. We are having difficulty locating the datasets for adverse reactions (Term/sym2/sym2), eligibility criteria (Registra/admin/admin), concomitant medications (Term/meds/meds), quality of life, laboratory values etc in the two submitted floppy discs (6/24/99). We request that you submit processed datasets of ALL raw data on case report forms. The processed dataset should be submitted in SAS transport files to the central document room as part of the NDA. In addition, please provide a list of all the datasets submitted and their corresponding event, page, module/view as in the annotated CRF. Please provide the definition of every variable in each dataset and the corresponding decodes. Comments on the adequacy of study design and efficacy endpoints of the required postmarketing study in

patients with Sporatic Adenomatous Polyposis will be forwarded to you when available.

- Additional requests:
    1. Please submit the original protocol of study 001 and all subsequent protocol amendments
    2. Please submit all data from pilot studies on biomarkers in humans, including protocols of these studies and all amendments.
    3. Please contact Mr. Paul Zimmerman to schedule a training session at the Agency to demonstrate how the videotape is reviewed according to the protocol.

October 7, 1999: Waiver for pediatric studies for this supplemental NDA granted under 21 CFR 314.55.

October 8, 1999: Training session on polyp counting and size measurement by Dr. Wallace from St. Mark's Hospital in London

- Dr. Wallace performed polyp counts and measurements for all patients (UT MD Anderson and St. Mark's Hospital)
- Still color photographs were the only medium used for enumeration and sizing of colorectal polyps. Videotapes served only as a reference for clarification of the photographic images, if needed and for the Committee's blinded *qualitative* assessment of response to treatment
- Rectum: One tattoo was placed in an area representative of polyposis. No polyps were removed from the tattoo area. Polyps outside of the tattoo areas were recorded by four still photographs at two areas with the highest density and two areas with the lowest density. These areas were not marked by tattoo. Only the polyps from the tattoo area are used to derive the primary efficacy endpoint.
- Colon: One or two tattoos were placed. In addition, two anatomical markers, the cecum (with the appendiceal orifice serving as the center), and the ileocecal valve, were used for the same purpose. No polyps in the tattoo areas and the cecum and ileocecal valve areas were removed.
- Duodenum: Ampulla was used as a marker. No effort was made to record the number of duodenal plaques and how much of the duodenum was covered by plaques. Two photographs, one high density, and one low density, of portions of the duodenum covered by plaque-like polyps were assessed, and percent area estimates were obtained by a single investigator using a standardized grid. These data were recorded on CRF No. 20.01 at baseline and CRF No. 55.01 at the end of study. The mean of the two measurements for each time point was computed and used to assess the secondary endpoint/variable, the percent change in the area of the duodenum

covered by plaque-like polyps. Additional information was obtained from the duodenal still photographs and polyp biopsies, and this was used to evaluate tertiary variables.

October 25, 1999: FDA requested the dataset on dietary assessment on all patients

October 25, 1999: Meeting with Searle and NCI to discuss the proposed SAP study and Barrett's esophagus study

November 3, 1999: Searle called to state that they planned to revise the indication and will not perform the study in SAP patients. A Phase IV study will be performed in FAP patients only.

November 10, 1999: Searle said that they could not provide the dataset on dietary assessment because these assessments were not recorded on case report forms.

November 12, 1999: Searle submitted the revised indication of "reduction and regression of adenomatous colorectal polyps in familial adenomatous polyposis patients"

November 17, 1999: FDA requested additional information and clarifications

November 23, 1999: FDA informed Searle that all original photographs on MD Anderson patients should be submitted for review. The photo prints on these patients in the sNDA were inadequate.

November 29, 1999: Teleconference to discuss Phase IV trial design. FDA stated the proposed single arm FAP study is unacceptable for the follow-up trial because there is no control arm, the proposed analysis using COX model is exploratory in nature, and the proposed clinical events that have been incorporated into a composite endpoint are not equal in their clinical significance.

December 1, 1999: FDA informed Searle that the photographs on all MD Anderson patients need to be provided for review by the Division in Rockville. It is not an option for a FDA representative to go to MD Anderson for this purpose.

December 3, 1999: FDA received photographs on MD Anderson patients.

December 6, 1999: Teleconference to discuss the proposed phase IV trial design.

December 9, 1999: Training session with Dr. Steinbach from MD Anderson
December 11, 1999: Teleconference to discuss the revised phase IV trial design
December 17, 1999: Teleconference to discuss the revised phase IV trial design

3. Manufacturing Controls

See CMC review by Dr. Kim.

4. Pharmacology

4.1. Overview

This section is a summary from NDA 21-156 Desk copy Volume 1.1 (NQ4-99-07-803 and BRD 99D 1947).

The major target of NSAIDs is the cyclooxygenase (COX) family of enzymes, which is involved in the first step of prostanoid synthesis from arachidonic acid. The two isoforms of this enzyme, COX-1 and COX-2, are more than 60% homologous but differ in two major aspects, the control of their expression and the conformation of the active site. Unlike COX-1 which is constitutively expressed, the expression of COX-2 is controlled by an inducible promoter. While COX-1 is involved in the homeostasis of various physiologic functions, COX-2 is responsible for many inflammatory processes (1).

A significant body of evidence suggests that the cellular expression of COX-2 is prominent in several types of tumors, including colon, skin, bladder, prostate, lung and mammary, as well as pre-cancerous changes such as Barrett's esophagus, the adenomatous polyp and actinic keratosis. In tissue culture models, overexpression of COX-2 is associated with increased invasiveness and other malignant phenotypic characteristics. The mechanisms through which NSAIDS and selective COX-2 inhibitors alter tumorigenesis are not well understood at the present time. Recent evidence suggested that the inhibition on tumor growth may be unrelated to the inflammation cascade. Studies have shown that Sulindac, one of the non-selective NSAIDs, induces apoptosis without decreasing local prostaglandin levels (2). Recent study of COX-2 inhibitors showed that inhibition of COX-2 produced sequential increases in arachidonic acid and

ceramide, the latter a potent stimulant of apoptosis (3). Furthermore, *in vitro* evidence exists that angiogenesis is regulated by COX-2 expression in colon cancer cells (4). Therefore, another mechanism by which tumor growth may be inhibited by COX-2 inhibitor is through blockade of angiogenesis and tumor vascularization.

CELEBREX is a nonsteroidal anti-inflammatory drug which selectively inhibits human recombinant COX-2 *in vitro* through a time-dependent mechanism that results in progressively increased inhibition at decreasing concentrations. At therapeutic concentrations in humans, CELEBREX does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme. CELEBREX reduces, in a dose-related manner, the production of prostaglandin E2 and prostaglandin I2 mediated by COX-2 at an inflammatory site *in vivo* (carrageenan injection into a rat air pouch). In contrast, CELEBREX has little effect on production of PGE2 in the rat stomach (reflecting COX-1 inhibition) demonstrating selectivity for COX-2 inhibition *in vivo*. The two major metabolites of CELEBREX do not inhibit either COX-1 or COX-2 *in vitro*.

CELEBREX was evaluated in two models of colon cancer. The Min mouse model represents a genetic model of human FAP. The administration of sulindac or piroxican in the drinking water prevents tumor development in Min mice.

Table 1: CELEBREX effect on the growth of tumors in Min mice

	Dosing: 30-80 days Tumors/mouse	Dosing : 55-80 days Tumors/mouse
Vehicle	22.4 ±9	22.9 ±7
CELEBREX 150 ppm	15.8 ±9	18.0 ±7
CELEBREX 500 ppm	15.8 ±5	16.3 ±6
CELEBREX 1500 ppm*	6.5 ±4	11.1 ±7
Piroxicam 50 ppm	5.2±4	7.9 ±5

* maximum effective concentration produced a mean Cmax ranging from 0.7-1.8 ug/ml.

Adenomas and adenocarcinomas of the colon can be chemically induced in rats by administration of azoxymethane (AOM). Many NSAIDs have been shown to prevent or inhibit colorectal tumor development in this model. Administration of CELEBREX for 11 weeks resulted in a 40% reduction in aberrant crypt foci that was similar to that observed for the positive control, Sulindac given at its MTD in the AOM model (5). Long term administration of CELEBREX at 1500 ppm (for one year following AOM induction) resulted in a 93% reduction in tumor incidence which surpassed the results observed in similar studies with a variety of

NSAIDs. In a subsequent study, CELEBREX was administered at 1500 ppm in the diet for 52 weeks after AOM induction. The approximate Cmax of CELEBREX at this dose was 3 ug/ml (6).

Table 2: CELEBREX effect on tumor incidence after AOM induction

	CELEBREX	Control
Incidence of tumors	6%	85%
Tumor multiplicity (#/animal)	0.06	1.91
Mean tumor volume (mm3)	27	204

Distribution studies in rats showed that the gastrointestinal tract was the tissue with the highest exposure to CELEBREX, whether given orally or intravenously (7). The concentrations of CELEBREX measured in large intestine at 1-8 hours postdosing were 2-16 fold greater than the concentrations in plasma. Therefore, local concentrations of the drug in the target tissue are achievable at doses that are effective in preventing colon cancer development in animal models.

4.2. Toxicology

See pharm/tox review by Dr. Schmidt for full discussion. The following discussion is based upon CELEBREX labeling in the Physician Desk Reference (PDR):

Carcinogenesis, mutagenesis, impairment of fertility: CELEBREX was not carcinogenic in rats given oral doses up to 200 mg/kg for males and 10 mg/kg for females (approximately 2- to 4-fold the human exposure as measured by the $AUC_{0\text{-}24}$ at 200 mg BID) or in mice given oral doses up to 25 mg/kg for males and 50 mg/kg for females (approximately equal to human exposure as measured by the $AUC_{0\text{-}24}$ at 200 mg BID) for two years.

CELEBREX was not mutagenic in an Ames test and a mutation assay in Chinese hamster ovary (CHO) cells, nor clastogenic in a chromosome aberration assay in CHO cells and an *in vivo* micronucleus test in rat bone marrow.

4.3. Pharmacokinetics

See Dr. Duan's review for details. The following is a summary from Celebrex label in the PDR and section NQ4-99-07-813 in the NDA.

Since the intravenous form of CELEBREX was not available, it was not possible to determine the absolute bioavailability of CELEBREX. Both peak plasma levels (Cmax) and area under the curve (AUC) are roughly dose-proportional across the clinical dose range of 100-400 mg studied. At doses higher than 900 mg there is less than proportional increase in Cmax and AUC under fasting conditions, which is thought to be due to the low solubility of the drug in aqueous media. This finding is consistent with the drug's biopharmaceutical classification, wherein the low solubility results in the dissolution-limited saturation in the absorption at high doses given on an empty stomach. However, when given with food, there was an excellent relationship between the dose and AUC (0-12) with multiple total daily doses of CELEBREX as high as 1200 mg. This finding may be explained by the fact that **dosing with food results in greater solubilization of CELEBREX due to increased secretion of bile and pancreatic fluid.**

The single dose pharmacokinetics of 200 mg CELEBREX are given in the following table. Peak plasma levels of CELEBREX occur approximately 3 hrs after an oral dose under fasting conditions. When CELEBREX capsules were taken with a high fat meal, peak plasma levels were delayed for about 1 to 2 hours with an increase in total absorption (AUC) of 10% to 20%. With multiple dosing, steady state conditions are reached on or before day 5. Co-administration of CELEBREX with an aluminum- and magnesium-containing antacid resulted in a reduction in plasma CELEBREX concentrations with a decrease of 37% in Cmax and 10% in AUC.

Table 3: Summary of Single Dose (200 mg) Disposition Kinetics of CELEBREX in Healthy Subjects[1]

Mean (%CV) PK Parameter Values				
Cmax, ng/mL	Tmax, hr	Effective t1/2, hr	Vss/F, L	CL/F, L/hr
705 (38)	2.8 (37)	11.2 (31)	429 (34)	27.7 (28)

[1]Subjects under fasting conditions (n=36, 19-52 yrs.)

In healthy subjects, CELEBREX is highly protein bound (~97%) within the clinical dose range. *In vitro* studies indicate that CELEBREX binds primarily to albumin and, to a lesser extent, α_1-acid glycoprotein. The apparent volume of distribution at steady state (V_{ss}/F) is approximately 400 L, suggesting extensive distribution into the tissues. CELEBREX is not preferentially bound to red blood cells.

CELEBREX metabolism is primarily mediated via cytochrome P450 2C9. Three metabolites, a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate, have been identified in human plasma. These metabolites are inactive as COX-1 or COX-2 inhibitors. Patients who are known or suspected to be P450 2C9 poor metabolizers based on a previous history should be administered CELEBREX with caution as they may have abnormally high plasma levels due to reduced metabolic clearance. Significant interactions may occur when CELEBREX is administered together with drugs that inhibit P450 2C9. *In vitro* studies indicate that CELEBREX is not an inhibitor of cytochrome P450 2C9, 2C19 or 3A4.

Clinical studies with CELEBREX have identified potentially significant interactions with fluconazole and lithium. Experience with nonsteroidal anti-inflammatory drugs (NSAIDs) suggests the potential for interactions with furosemide and ACE inhibitors. The effects of CELEBREX on the pharmacokinetics and/or pharmacodynamics of glyburide, ketoconazole, methotrexate, phenytoin, and tolbutamide have been studied *in vivo* and clinically important interactions have not been found.

CELEBREX is eliminated predominantly by hepatic metabolism with little (<3%) unchanged drug recovered in the urine and feces. Following a single oral dose of radiolabeled drug, approximately 57% of the dose was excreted in the feces and 27% was excreted into the urine. The primary metabolite in both urine and feces was the carboxylic acid metabolite (73% of dose) with low amounts of the glucuronide also appearing in the urine. It appears that the low solubility of the drug prolongs the absorption process making terminal half-life ($t_{1/2}$) determinations more variable. The

effective half-life is approximately 11 hours under fasted conditions. The apparent plasma clearance (CL/F) is about 500 mL/min.

Pediatric Use: CELEBREX capsules have not been investigated in pediatric patients below 18 years of age.

Race: A Meta-analysis of pharmacokinetic studies has suggested an approximately 40% higher AUC of CELEBREX in Blacks compared to Caucasians. The cause and clinical significance of this finding is unknown.

Geriatric Use: At steady state, elderly subjects (over 65 years old) had a 40% higher Cmax and a 50% higher AUC compared to the young subjects. In elderly females, CELEBREX Cmax and AUC are higher than those for elderly males, but these increases are predominantly due to lower body weight in elderly females.

Hepatic Insufficiency: A pharmacokinetic study in subjects with mild (Child-Pugh Class I) and moderate (Child-Pugh Class II) hepatic impairment has shown that steady-state CELEBREX AUC is increased about 40% and 180%, respectively, above that seen in healthy control subjects. Therefore, CELEBREX capsules should be introduced at a reduced dose in patients with moderate hepatic impairment. Patients with severe hepatic impairment have not been studied. The use of CELEBREX in patients with severe hepatic impairment is not recommended.

Renal Insufficiency: In a cross-study comparison, CELEBREX AUC was approximately 40% lower in patients with chronic renal insufficiency (GFR 35-60 mL/min) than that seen in subjects with normal renal function. No significant relationship was found between GFR and CELEBREX clearance. Patients with severe renal insufficiency have not been studied.

A population pharmacokinetic model was developed to describe the pharmacokinetics of CELEBREX in osteoarthritis and rheumatoid arthritis patients. The pharmacokinetic model was based on 326 CELEBREX plasma concentrations from 100 patients receiving multiple doses of CELEBREX 50, 100, 200 or 400 mg bid in two phase III trials. A steady-state one-compartment model adequately described the CELEBREX plasma concentrations in these patients. Results of the covariate analysis identified race and body weight as influential factors on CL/F. The increases in steady-state plasma CL/F of CELEBREX were nearly proportional with increases in body weight. The population mean estimate (% CV) for Caucasians was 30.0 (50) L/hr/70 kg, which is in good

agreement with the estimated CL/F value obtained in the young healthy adult subjects.

CELEBREX pharmacokinetic parameters in patients with FAP were compared to those in patients with OA and RA. Blood samples for CELEBREX determination were obtained at trough at the 3 and 6-month visits. Due to the limitations with a trough sampling design, a **population pharmacokinetic model was not developed for the FAP patient population.** However, a comparison of the PK data in the FAP population to the OA/RA patient population was performed using a population pharmacokinetic model developed to describe the pharmacokinetics of CELEBREX in OA and RA patients. A population PK model for CELEBREX plasma concentrations obtained from OA and RA patients receiving 50, 100, 200 or 400 mg BID CELEBREX was employed to obtain estimates of CELEBREX CL/F in FAP patients. A steady-state one-compartment model with first-order absorption and elimination was used to describe the CELEBREX steady-state plasma concentrations in the OA and RA patients. Estimates of the population mean parameters and variance components (% CVs) were made using the base and final (including covariate effects for race and body weight) models. Based on the parameter estimates from the final model for OA and RA patients, empirical Bayes estimates of the CELEBREX CL/F for the FAP patients were obtained. The empirical Bayes estimates were obtained using nonlinear mixed effects methodology (first-order conditional error) as implemented in the NONMEM software. The applicant reported that the CELEBREX plasma concentrations in FAP patients were in good agreement with the predictions based on the population model developed from the OA and RA patients. The estimates of CELEBREX plasma CL/F in the FAP patients were very similar to the estimates for the OA and RA patients and were consistent with the population mean estimates of 28.3 L/hr based on the OA/RA population PK analysis.

The applicant did not perform pharmacodynamic analysis to explore the relationship between patient demographics, concomitant medications, laboratory values (e.g., albumin, creatinine clearance, liver enzymes) and the pharmacokinetic parameters. No information was provided on the relationship between selected adverse events and systemic exposure. No regression analysis was provided to look for the relationship between efficacy-related endpoints and systemic exposure as measured by volume of distribution and total clearance.

5. Clinical Background

Sporadic forms of colon cancer account for more than 90 percent of all colon cancers each year. Most such cancers arise from adenomatous polyps, an intermediate premaligant stage. In contrast, the hereditary polyposis syndromes, further classified as adenomatous polyposis and hamartomatous polyposis syndromes, make up approximately 1 percent of colon cancers annually. The hereditary nonpolyposis colorectal cancer syndromes are believed to account for 5 to 10 percent of colon cancers every year (8).

The hereditary polyposis syndromes are differentiated on the basis of histologic criteria, i.e., those that express adenomatous polyposis and those that exhibit multiple hamartomatous polyps. The adenomatous polyposis syndromes include familial adenomatous polyosis (FAP), Gardner's syndrome (GS), and Turcot's syndrome.

FAP is characterized by the presence of hundreds to thousands of colorectal adenomatous polyps and the inevitable development of colon cancer if left untreated. Adenomas often occur in the upper gastrointestinal tract as well. If FAP occurs with extraintestinal lesions, classically osteomas or benign soft tissue tumors and cysts, the disorder is called GS. In common usage, FAP is often used to refer to all patients with inherited adenomatous polyposis, both FAP and GS (9). Turcot's syndrome is defined as the occurrence of central nervous system tumors associated with colonic adenomatosis polyposis. This syndrome is considered separately because of recent evidence that it does not arise from APC gene mutations. Attenuated adenomatous polyposis coli (AAPC) represents a variant of FAP that arises from mutations in the APC gene. It is expressed as a variable number of colonic adenomas, usually less than 100.

FAP is an autosomal dominantly inherited disorder with an 80% to 100% penetrance. The disease results from germ line mutations of the APC gene. The frequency of the FAP gene has been estimated on the basis of disease prevalence to be 1 in 5000 to 1 in 7500 (10). Men and women are affected equally by this disease. It is estimated that one third of newly diagnosed cases (i.e., those not belonging to previously identified families) appear to represent new mutations.

The APC gene is located on the long arm of chromosome 5. The coding portion of the gene contains 8538 base pairs and gives rise to an approximately 300 kd protein with 2843 amino acids. Expression of the APC protein is found in many other tissues, and mutations of the APC

gene have been described in malignancies other than colon cancer. The majority of FAP families tested have been found to have unique and different mutations of the APC gene. Although these different mutations are found scattered throughout the gene, a unifying feature is that they almost all result in truncation of the APC protein. These truncated APC proteins have been found to oligomerize to the normal or wild type protein. The current hypothesis is that the truncated protein inactivates the protein from the normal allele by dominant negative inhibition. The APC gene is thus believed to be a tumor suppressor gene. Tissues from sporadic adenomas and cancers of the colon often exhibit APC gene mutations. In this setting, the mutations are acquired rather than inherited, because they are not found in normal tissues. The tumor mutations are nonetheless almost all mutations that cause truncation of the protein, similar to the inherited mutations of FAP. Inherited APC mutations result in FAP, whereas **acquired APC mutations are an early and integral step in sporadic adenomas and colon cancer.** Environmental factors do not appear to be of primary importance in the pathogenesis of FAP. Nonetheless, there is evidence that the genetic defects of FAP are modulated by certain environmental factors. Polyps, for example, have been seen to resolve after subtotal colectomy, pregnancy, oral calcium, oral fiber and oral sulindac (9)

Data from polyposis registries indicate that the average age of patients at the onset of polyps is 25 years, at the onset of symptoms (gastrointestinal bleeding and abdominal pain) 33 years, at diagnosis 36 years and at diagnosis of colon cancer 42 years (11). The hallmark of the FAP phenotype is the presence of **100 or more** colonic adenomatous polyps, although the average number of adenomatous polyps in a person with fully expressed FAP is 1000, with some persons exhibiting more than 5000 polyps. The number 100 was originally established as a diagnostic reference because no one with fully developed FAP in the St. Mark's registry had fewer than this number and no one with sporadic adenomas had more than 100 polyps. Rectum colonoscopic surveys have confirmed that it is unusual to find more than 6 polyps and rare to find more than 50 polyps in persons with sporadic adenomas.

Polyposis usually develops in the second or third decade of life. The mean age of polyp occurrence assessed by rigid sigmoidoscopy in a study that combined the St. Mark's and Perth FAP registries was 15.9±5.4 years. Polyps are distributed evenly throughout the colon, with a slight distal colonic excess. The size of the polyps depends on the stage at which the patient is examined. Even in fully developed cases, **90% of adenomas are less than 0.5 cm in diameter.** Less than 1% of polyps are larger than 1 cm in diameter at the stage. Two patterns of polyp formation are

recognized. The carpeting pattern is characterized as myriads of tiny polyps which uniformly cover the entire surface of the colon. Also seen is a pattern of more discrete, but fewer, polyps which are slightly larger. The colonic polyps in FAP are usually tubular adenomas, indistinguishable from common or sporadic adenomas. Villous and tubulovillous histologies are also seen with much less frequency and in larger polyps. **A histologic feature of FAP not observed in the general population is dysplastic or adenomatous epithelia cells in single crypts or even portions of single crypts. Such structures are called microadenomas. They are often seen in biopsy specimens of normal appearing flat mucosa in individuals with FAP.** Gastric polyps occur in 30% to 100% of FAP patients. In the gastric fundus and body, the polyps are nonneoplastic fundic gland polyps. The polyps are sometimes so numerous that they coalesce, forming areas of irregular, matted surface mucosa. Fundic gland polyps rarely cause symptoms and do not appear to have malignant risk. Adenomatous polyps may also occur in the stomach of persons with FAP, but are almost always confined to the gastric antrum. They are commonly observed in FAP patients in Japan but are very unusual in other countries. There is little, if any, increased risk of gastric cancer in FAP patients outside Japan. Duodenal polyps are found in 46% to 93% of polyposis patients. The polyps are multiple adenomas, 1 to 5 mm in diameter, and are almost always asymptomatic. There is a significant risk of malignancy in the duodenum, with a 4% to 12% lifetime incidence of duodenal cancer. This frequency is estimated to be more than 300-fold greater than that of the general population. **Some studies find the risk of duodenal cancer to be greater than that of rectal cancer in patients** who have had a subtotal colectomy with ileorectal anastomosis. Upper gastrointestinal cancer has been reported to occur in 4.5% of FAP patients, with an average age at diagnosis of 52 years. The average age at diagnosis of periampullary cancer in patients with polyposis is 46 years. The duodenal papilla has a particular propensity for adenomatous change in polyposis patients. More than one third of the duodenal cancers reported occur at the papilla and the risk of malignancy is more than 100-fold greater than in the general population. Obstruction of the pancreatic duct has been observed from benign and malignant tumors of the papilla. These papillary neoplasms may account for the excess incidence of pancreatitis reported in some series of FAP. Reports from Japan have revealed jejunal adenomatous polyps in up to 40% and ileal polyps in 20% of those with FAP. The polyps occur throughout the small bowel but are concentrated for the most part in the proximal jejunum and distal ileum. Transformation to malignancy is very unusual but a few cases of small bowel cancer distal to the duodenum have been reported. Adenomatous polyps are also known to occur, possibly with increased frequency postoperatively, in the distal ileum after subtotal colectomy, colectomy with ileostomy, and colectomy with ileoanal pull-

through. Distal ileal cancer has been reported in these settings but it is rare. Gallbladder and bile duct adenomas and cancer have also been reported, as has pancreatic cancer, but these appear to be very rare.

The justification for screening as a method of cancer prevention in FAP is well established. The cancer risk in FAP patients presenting with symptoms varies from 32% to 57%. Cancer is almost never present at the time of polyposis diagnosis in patients who undergo interval prospective screening. **Appropriate screening could conceivably prevent all colon cancer in persons known to be at risk of FAP.** This outcome depends mostly on family notification and regular follow-up. Screening of FAP should be done by video or fiberoptic endoscopy because of the usual small polyp size and the requirement of histology for diagnosis. Children of affected parents should be screened regularly to detect the emergence of colonic polyposis. Flexible proctosigmoidoscopy is sufficient for screening and examinations should begin by 10 to 12 years of age and should continue every 1 or 2 years until 35 years of age. Thereafter, examinations should be performed every 3 years. Full colonoscopy should be performed on the person who is first diagnosed with polyposis that is already well developed, because larger polyps and malignancy may be present in the proximal colon in this situation. Genetic testing for FAP using the DNA obtained from peripheral blood samples is available at regional DNA diagnostic laboratories. Testing employs DNA linkage markers to the APC gene. The use of linkage markers requires that two family members already have a firm diagnosis of FAP. Such markers can diagnose more than 95% of persons at risk of FAP, with greater than 98% accuracy. A method for detection of abnormal APC protein is available and can detect up to 87% of gene carriers. Genetic testing should first be performed at 10 to 12 years of age. Those who test positive should undergo sigmoidoscopy, as has been outlined, to examine for the development of adenomas. Patients testing negative should nonetheless have sigmoidoscopy every 3 to 5 years until 40 years of age. As genetic testing provides 100% accuracy, follow-up of this group becomes unnecessary. Upper gastrointestinal screening should begin when the diagnosis of colonic polyposis is made. Screening consists of upper gastrointestinal endoscopy every 1 to 3 years. The longer interval is adequate if polyps are not present. Their presence of antral or duodenal adenomas, and especially adenomatous change on the duodenal papilla, justifies endoscopic inspection every 1 or 2 years, depending on the number and size of polyps.

The average life expectancy for patients with untreated FAP has been estimated to be 42 years. Life expectancy is thought to be much longer with colectomy, but accurate figures are not available. The major causes of death after colectomy are upper gastrointestinal cancer and desmoid tumors. Thirty-six FAP patients were identified from Cleveland Clinic

records who had undergone total or subtotal colectomy and died at some time thereafter. The major causes of death in that group were desmoid tumors, in 11 (31%), periampullary cancer in 8 (22%); rectal cancer in 3 (8%), adrenal cancer in 1 (3%), and carcinomatosis in 1 (3%). Those with desmoid tumors died an average of 6.6 years after colectomy, whereas those with periampullary cancer died an average of 23.1 years after surgery.

Surgical therapy is the only acceptable option for patients with FAP after colonic polyps have been detected. Its timing depends on psychosocial issues and counseling, and is delayed whenever possible until the patient reaches his or her 20s. Historically, subtotal colectomy with ileorectal anastomosis was performed, leading to **spontaneous regression of rectal polyps in 64 percent of patients** (12). However, nearly 50 percent of patients had a recurrence of rectal polyps, with a risk of adenocarcinoma (13). As a result, about 25 percent of patients later required proctectomy. Subtotal colectomy with ileorectal anastomosis is a relatively simple procedure, with mortality of less than 1% and morbidity less than 10%. The primary concern with this procedure is continued adenoma formation in the rectum and attendant cancer risk. Sigmoidoscopy with ablation of recurrent adenomas is therefore needed every 3 to 6 months. Despite planned follow-up, the incidence of rectal cancer is reported between 6% at 20 years and 55% at 30 years after postsurgery (14). Up to 30% of these postsurgical patients also need eventual rectal resection because of inability to control polyps medically. Colectomy with mucosal proctectomy and ileoanal pouch has been introduced as a method of complete colonic mucosal removal that retains rectal function. This procedure now is considered the procedure of choice in many centers. Several problems, however, are more common than with ileorectal anastomosis, including more nighttime incontinence and more sexual dysfunction. An intermediate approach has been suggested that includes selecting patients with fewer rectal polyps for ileorectal anastomosis and then later revision to ileoanal pouch if warranted. Total colectomy with ileostomy was advocated as an alternative, but there were psychological problems, especially in young patients, in contending with the cosmetic and mechanical aspects of the ileostomy bag. At present, experienced surgeons recommend colectomy with mucosal proctectomy followed by ileoanal anastomosis in two stages (15). This surgical option is suitable for young patients. In contrast, one can consider subtotal colectomy with ileorectal anastomosis for patients with few rectal polyps if there is vigilant follow-up.

The management of upper gastrointestinal polyps is more problematic, since long-term studies of polyp treatment only recently have begun. It is agreed that radical surgical treatment is not indicated for numerous small

gastric or duodenal polyps alone. Villous adenomas, large tubular adenomas (>5 mm), and symptomatic adenomas, regardless of histology, warrant removal because of the potential for malignant change and nonmalignant complications (16).

6. Pivotal trial

There is one pivotal trial (Study 001) submitted in the supplemental NDA. This is a randomized, double-blind, placebo-controlled, three-arm parallel group trial conducted in patients with FAP with or without colectomy. The applicant intends to demonstrate the efficacy and safety of CELEBREX (SC-58635) to regress and prevent colorectal and duodenal polyps in patients with FAP.

6.1.Protocol Review

6.1.1. Protocol Overview

Investigators: Dr. Gideon Steinbach et al
Study Center(s): MD Anderson Cancer Center in the US and St. Mark's Hospital in London, UK

Studied Period (years): December 20, 1996 and November 22, 1998
Data /cut-off date: Not provided by the applicant

Review of Protocol Amendments:

There were four amendments and three administrative changes to the Protocol and one amendment to the Statistical Analysis Plan.

- Protocol Amendment No. 1 (January 15, 1997): multiple text changes and additions; modifications of inclusion/exclusion criteria; adding criteria for discontinuing from the study due to allergic reactions; clarifications on the methodology in polyp counting and biomarker studies; adding family history assessment and pedigree worksheet in baseline evaluations
- Protocol Amendment No. 2 (January 15, 1997): text changes for clarification purposes; adding the requirement for a urine pregnancy test within 14 days prior to baseline randomization; adding gastric biopsies to the laboratory evaluations; making changes to the Informed Consent Document; deleting the requirement that Committee members review the "cloverleaf" pictures to derive the primary efficacy endpoint; adding a requirement for assessing duodenal polyps: two still photos would be taken

of each of the two areas of greatest polyp burden and two photos of each of the two areas with least polyp burden outside the filed of the ampulla. The biopsy forceps would be held open next to the largest and then next to the second largest polyp in each field.

- Protocol Amendment No. 3 (October 15 1997): changing the exclusion criterion on bilirubin elevation from >1.2 times upper limit of normal (ULN) to >2 times ULN; changing the number of still photographs taken for the assessment of rectal and duodenal polyps from two to one
- Protocol Amendment No. 4 (August 31 1998): modifying the protocol text regarding the telephone follow up to month 7-8 (±10 days) for all patients who have completed the study; changing the primary efficacy variables to percent change from baseline in the number of polyps in the colorectum and the percent change in the area of plaque-like duodenal polyps; changing the method of analysis of all continuous outcome measures to the two-sample Wilcoxon nonparametric test to compare CELEBREX 400 milligrams (mg) twice a day (BID) to placebo at the 0.05 significance level and adding that the p-values for the comparison of CELEBREX 100 mg vs. placebo and CELEBREX 100 mg to CELEBREX 400 mg were considered secondary information
- Protocol Administrative Change No. 3 (February 16, 1999): redefining the surgical status of patients (CRF 4) due to differences in the standard of care and definitions used in the United States (US) versus the United Kingdom (UK): subtotal colectomy (patients who have had an ileorectal anastomosis or any portion of the colon surgically removed); total colectomy (patients who have had an ileoanal anastomosis or an ileoostomy with no colorectal remnants); partial colectomy was equated with subtotal colectomy; adding a new CRF so that drug administration times and genetic testing data could be entered into the database
- Amendment to the Statistical Analysis Plan (December 8 1998): defining one primary endpoint, i.e., percent change from baseline for the number of colorectal polyps, one secondary endpoint i.e. percent change in area of duodenal plaque-like polyps, and all other variables as tertiary variables. The key statistical comparisons were CELEBREX 400 mg BID vs. Placebo (type I error of 0.04) and CELEBREX 100 mg BID vs. Placebo (type I error of 0.01). All randomized patients were to be included in the Intent-to Treat (ITT) analysis and rules for missing data were established. For five discontinued patients with no data beyond baseline all % changes from baseline scores for the primary endpoint will be defined as 0%. Relative to the secondary endpoint, there are two

patients with no duodenal plaque at baseline and some duodenal plaque at end of study. Since the % change from baseline for these patients can't be determined, the baseline value will be defined as 1 % for both these patients.

6.1.2. Study Design

This randomized, double-blind, placebo-controlled, three-arm parallel group trial was sponsored by the National Institutes of Health (NIH) /National Cancer Institute (NCI) and was designed to determine the efficacy and safety of CELEBREX (SC-58635) to regress and prevent colorectal and duodenal polyps in patients with FAP. Eighty-one (75 with lower GI tract disease and 6 with only duodenal lesions) patients and an additional 2 replacement patients were enrolled in the study for a total of 83 patients. Patients with lower GI tract disease were randomized by center, using a ratio of 1:2:2 (placebo, CELEBREX 100 mg BID, CELEBREX 400 mg BID, respectively). The six patients with duodenal disease only were randomized using a ratio of 1:1:1 (placebo, CELEBREX 100 mg BID, CELEBREX 400 mg BID, respectively). Duration of treatment was six months (up to 200 days). Each center utilized its own FAP registry as well as other registries for recruitment, thus approximating a larger, multi-centered study.

6.1.3. Objectives

- Determine the efficacy of CELEBREX in inducing the regression of colorectal and duodenal polyps in patients with FAP, and
- Determine the relative tolerability and safety of CELEBREX in FAP patients.
- Investigational Endpoints
  - Data will be obtained on the appearance, number and distribution of aberrant crypt foci and microscopic adenomas observed by magnifying and chromoendoscopy at baseline and after treatment
  - To determine the relative effects of the study drugs and placebo on colonic COX-1 and COX-2 mRNA and protein levels, as well as the effects on colonic eicosanoid levels in biopsy tissue from colonic polyps and normal mucosa
  - To determine the relative effects of the study drugs and placebo on the three-dimensional colonic crypt morphology and on crypt cell proliferation and apoptosis. The 3-D crypt morphology and the number and spatial distribution of M-phase and apoptotic cells would be determined by confocal microscopy in intact microdissected crypts from normal appearing mucosa of FAP

patients at baseline and after six months of treatment with the study drug. The effects of the study drug on apoptosis in polyp tissue would be studied by immunohistochemistry. In a subset of patients, colonic crypts would be analyzed for S-phase cell number and spatial distribution by histone H3 *in situ* hybridization and confocal microscopy.

- To correlate response or resistance to the study drugs with specific genotypes of APC mutations. Genotyping of all patients will be initially performed by the in vitro synthesized protein (IVSP) method followed by nucleotide sequencing in those with informative IVSP. Sequencing of the first four exons of APC will be performed in patients with the attenuated phenotype.
- To correlate polyp response or resistance to the study drugs with polyp p53, Ras, and bcl-2 expression determined by immunohistochemistry.

6.1.4. Patient population:

75 randomized patients had evaluable colon and/or rectal segments, and six additional patients had duodenal polyps but no evaluable colorectum. These 75 patients would undergo endoscopy and biopsies of the full extent of their colorectum, and esophagogastroduodenoscopy at baseline and at six months. The six patients without assessable colorectal polyps, including patients with total colectomy and ileoanal anastomosis, who are known to have duodenal polyps will undergo esophagogastroduodenoscopy at baseline and at six months. Enrollment was blocked by site using a block size of five. It was anticipated that all patients would begin drug treatment during months 1-11 of the study (seven per month). Patients who dropped out after study drug administration due to adverse events would not be replaced. Patients who have received study drug and dropped out for reasons other than adverse events or patients who dropped out prior to receiving study drug may be replaced at the discretion of the Sponsor. Telephone interview would be conducted at month 8 for patients with adverse events at termination.

To qualify for randomization, candidates must fulfil the following criteria:

- 18 to 65 years of age; willing and able to sign informed consent; women of childbearing potential must not be pregnant, lactating and must agree to used adequate contraception during the study
- Had a diagnosis of FAP based on any of the following criteria:
  - >100 polyps; or

- >10 polyps and age ≤40 years, or >25 polyps and age >40 years and characteristic family history (autosomal dominant pattern) which included one of the following:
  - >100 polyps in a first degree family member; OR
  - >25 polyps in two relatives in two generations, including a first degree family member; OR
  - genetic diagnosis in a relative
- Genetic diagnosis by *in vitro* synthesized protein (IVSP) or similar assay. Patients with a new molecular diagnosis of FAP without previous documentation of adenomas were eligible for enrollment and for the baseline colonoscopy and upper endoscopy, and could remain on study and receive the drug treatment only if ≥2 adenomas were documented by histopathology;
- Had an endoscopically assessable colonic and/or rectal segment or assessable duodenal polyps remaining after baseline endoscopy and polypectomy as follows

  Rectum: Five or more polyps ≥2 mm diameter including three quantifiable polyps ≥3mm diameter or two quantifiable polyps ≥ 5 mm diameter

  Colon: Five or more polyps ≥2 mm including: three quantifiable polyps ≥3 mm diameter, or two quantifiable polyps ≥5 mm diameter. (In the colon, quantifiable polyps were defined as being within a composite "cloverleaf" photograph that included a tattoo, the appendix, or the ileocecal valve.);

  Duodenum: Stage III or IV polyp burden according to Spigelman Criteria (see protocol, Appendix 17.6), OR satisfaction of both the following criteria:
  - ≥2 polyps are ≥3 mm in diameter; and the sum of the diameters of the polyps ≥2 mm was ≥11 mm, or one polyp was ≥9 mm in diameter.

- Hb≥10 g/dl, platelet count >100,000/ul, WBC≥3,000/ul, SGPT≤1.5 x upper limit of normal, SGOT≤1.5 x upper limit of normal, alkaline phosphatase ≤1.5 x upper limit of normal, bilirubin ≤2 x upper limit of normal, creatinine ≤1.5 x upper limit of normal

Candidates were not eligible if any of the following applied:
- An anticipated colectomy within eight months of randomization;
- A partial or complete colectomy within 12 months prior to enrollment;

- The use of any NSAID, including aspirin, at any dose during the six months prior to study entry. (Use of an NSAID at any dose at a frequency averaging ≥3 times a week during the six months prior to study entry required a six-month washout period prior to eligibility beginning with the time of the patient's last dose. Use of an NSAID at any dose at an average frequency of one to two times per week during the six months prior to study entry required a three-month washout period, beginning with the time of patient's last dose);
- A history in the past year of discrete gastric or duodenal ulcer of ≥ 5 mm in size, except that patients with a history of H. pylori-related peptic ulcer disease became eligible for study participation upon successfully completing antibiotic treatment of H. pylori;
- A history of invasive carcinoma in the past five years other than resected Duke's A/B1 colon cancer or resected non-melanomatous skin cancer;
- A history of hypersensitivity to COX-2 inhibitors, sulfonamides, NSAIDs, or salicylates;
- An inability to return for follow-up tests;
- Use of investigational agent within the last 3 months, or at the decretion of the medical monitor
- Significant medical or psychiatric problems, including significant renal, hepatic, or hematologic dysfunction, which would have made the patient a poor protocol candidate
- Has had a positive serum/urine pregnancy test within 14 days prior to baseline randomization

6.1.5. Randomization

Randomization of colorectal patients was blocked by site. Patients with duodenal-only disease were separately randomized, two per treatment group. The colorectal patients were randomized using a ratio of 1:2:2, that is, the CELEBREX 100 mg BID and 400 mg BID groups were randomized to have double the number of placebo patients. The randomization code was generated by Searle according to criteria detailed in the statistical section. The first patient at each site was assigned the lowest randomization number, and subsequent patients received the next higher randomization number and received corresponding study drug. The drug was labeled and packaged in a sequential order. Each study site received an identical randomized block of study drug for the six patients who only had duodenal polyps. The two sites contacted each other immediately when the study drug was dispensed so that no patient number was used twice. All patients with duodenal-only polyps were entered at MDACC. All

study personnel were blinded to the study drug administration. In the event of an adverse event or other circumstance requiring unblinding, the Principal Investigator would contact the NCI Medical Monitor for permission to unblind. Should the NCI Medical Monitor be unavailable and the patient required emergency care, the Principal Investigator may break the code. The date and reasons for breaking the code must be submitted to the NCI by the Principal Investigator as soon as possible. A patient would be immediately withdrawn from the study if the code was broken.

6.1.6. Treatment Plan

Patients were instructed to take two capsules (50 mg or 200 mg CELEBREX or placebo) orally with their morning meal and two capsules orally with their evening meal. The Treatment Period was defined as the 6 month period (up to 200 days) after the first dose of study medication and was six months (200 days) for all three arms. There was no dose reduction allowed. Drug treatments were held for any grade 3 or higher toxicities or grade 2 or higher hepatic or renal toxicities except SGOT or SGPT or alkaline phosphatase increases to grade 2 or 2 x baseline value, whichever is higher; and for creatinine or bilirubin increases to grade 2 or 1.5 x baseline value, whichever is higher.

Patients would be withdrawn from the study for any of the following reasons: the patient withdrew consent; disease progression; Grade 4 toxicity; allergic reaction to the study drug with a severity Grade 2 or higher based on NCI Common Toxicity Criteria; at the discretion of the Principal Investigator; or a diagnosis of cancer or other serious illness. All patients leaving the study prior to study completion were asked to return to the study site and complete all end of study procedures as outlined above.

Re-challenge of the patient was allowed only after the initial toxicity had been resolved to the satisfaction of the Principal Investigator. If toxicity recurred, the patient would be dropped from the study. Study medication was stored at ambient temperature. Patient compliance was measured by counting the number of capsules in the returned bottles at each visit (primary measure) and patient recorded pill diaries (secondary measure).

6.1.7. Evaluations during study

Scheduled events are listed in table 4. The Telephone System Assessment Worksheets were completed at Weeks 2 and 4 and then monthly for 5 months and at 7 to 8 months (±10 days). A follow-up telephone assessment off drug intervention was conducted at eight months after the patient completed the study. These structured questionnaires elicited adverse event information by requiring all patients to respond affirmatively or negatively to a comprehensive list of potential events. Part 1 of the questionnaire was a general list of body systems. If a patient admitted a problem with any system, Parts 2 and 3 of the questionnaire were to be completed. Potential drug-specific toxicities were interspersed in the review and were the same for all study groups. Patients with drug-related symptoms were interviewed at weekly intervals until symptoms resolved or more frequently per clinical evaluation by the study physician. Any adverse event with a severity grade 2 or higher based on the NCI Common Toxicity Criteria was communicated directly to the Principal Investigator, who made a determination regarding the proper course of action as detailed in Section 9.0 of the protocol. At 1 month and 3 months (90±10 days), clinical laboratory evaluations were conducted after an approximate 12-hour fast. Drug trough assessments, a SF-36 Health Survey (country specific, standard), and urinalysis were performed at three months (90±10 days). Compliance monitoring (e.g., recent pill intake, pill count, review of the patient's medication list) was included in the history and symptom review form. At the completion of the treatment period, Month 6/Termination endoscopy and videotaping were performed as described at baseline to obtain data for efficacy evaluations, and polyps were removed, if available (after the videotapes and still photographs were completed). In addition, one biopsy was taken from up to four sites of presumably regressing polyps (such sites are described as pink halos) if found on follow-up endoscopies. These were analyzed for crypt morphology and apoptotic index, p53, COX messenger ribonucleic acid (mRNA)/protein, and immunohistochemistry.

Reviewer's comment: Data from these biopsy evaluations were not included in the clinical and safety databases.

Table 4. Schedule of Observations and Procedures

Evaluation/Procedure	Registration	Baseline	Month 1	Month 3	End of Study (Six months) or Early Withdrawal
Informed Consent	X				
Inclusion/Exclusion	X	X			
Medical History	X				X
Physical Exam	X				X
Lab Evaluations		X [a]	X [b]	X [b]	X [a]
Drug Trough Levels		X		X	X
Serum/Urine Pregnancy Test [c]		X			
Serum Test for H. pylori		X			
Genetic Screen (APC gene mutation)		X			
Colonoscopy/sigmoidoscopy and biopsies [d]		X			X
Esophagogastroduodenoscopy (EGD) and biopsies		X			X
Concomitant Medication		X		X	X
Dispense/Record Study Medication [e]		X		X	X
Dietary Assessment (Harvard Willett semiquantitative food frequency questionnaire)		X			X
Quality of Life - SF-36 Health Survey (country specific, standard) [f]		X		X	X
Telephone Symptom Assessment Worksheet [g]		X	X	X	X
Adverse Events				X	X
Family History and Pedigree Worksheet		X			

a. Includes hematology, chemistry, PT, PTT, and urinalysis.
b. Includes hematology, chemistry; urinalysis performed at Month 3 only.
c. Serum/urine pregnancy test within 14 days before the first study drug administration.
d. Six patients who had duodenal polyposis alone did not undergo colorectal endoscopies.
e. Drug was dispensed every 50 days until completion of six month treatment period.
f. Was completed prior to any invasive procedures.
g. Weeks 2 and 4, then monthly for five months, and at seven to eight months (±10 days).

Preparation for procedures:

- Colonoscopy or sigmoidoscopy: NuLYTELY 16 oz two evenings prior to procedure; low fiber diet on the preceding day; NuLYTELY 1 gallon on the preceding evening; an overnight fast
- EGD: an overnight fast

Lower GI Evaluations by colonoscopy/sigmoidoscopy: The entire colon and/or rectum were visualized and recorded on videotape. All endoscopies were performed with the same set of pre-marked endoscopy forceps that had been verified by the endoscopist. All polyps≥1 cm would be removed with cautery snare or cautery biopsy when possible.

Rectum: Videotaping was performed with full insufflation of the rectum with the open biopsy forceps (6 mm in size) in the field of view (except

when the channel is used for other purposes) and with a recorded voice. All pertinent information was dictated for audiorecording simultaneously with the video procedure. Location and picture number were recorded when still photos were taken. When still photographs were taken, the open biopsy forceps or endoscopic measure was held against the rectum wall, and the location and picture number were recorded. An area near the mid-rectum (chosen where full circumferential view is easily attainable) representative of **the highest polyp burden** is chosen and a small sterile **India ink tattoo** was made. The scope was then advanced to the third valve of Houston (if clear) or to the rectosigmoid juncture. The rectum was then videotaped in a spiral fashion up to the anal verge. When available, 12 polyps were removed with serial biopsies. In most cases, those polyps would be completely excised by the biopsy procedure. The two areas of highest polyp burden were avoided if possible. Five or more unbiopsied polyps of >2 mm or five polyps of > 3 mm (of the largest size available) were left. After taking the polyp biopsies, the rectum was washed and the endoscopy stopped for 5-10 minutes until all blood staining resolved. The video procedure was then repeated (second time). 10 cc of indigo carmine was sprayed on the rectal walls and the residue suctioned. The rectum was kept insufflated and the video procedure repeated (third time).

A still color photograph was taken with the tattoo in the center as well as four photos with the tattoo at each of the four mid-edges of the field. These five photos were mounted into a composite **"cloverleaf"** photo to allow a larger visual re-creation of the photographed mucosa than would be otherwise available via any single photo. **These photos served as the "source documents" for definitive polyp measurements.** The open biopsy forceps was held next to the largest polyp in each field. Also, the closed forceps was photographed next to the smallest polyp.

One still photo was taken of the area of greatest polyp burden and the area of the least polyp burden outside of the field of the tattoo, with the biopsy forceps held open next to the largest and second largest polyp in each of these fields.

Rectal polyp counting: There were five still photographs at the site of the rectal tattoo. One with the tattoo in the center (photographs RC), and four with the tattoo at the middle of each of the four edges (photographs RT, RL, RB, RR). Using the open biopsy forceps in the photograph as a measure, a 3 cm diameter circle was drawn with the tattoo at the center (photo a), or with the tattoo on the circumference of the photo (photo b-d). The photograph with the tattoo at the center served as the primary quantitative endpoint. The following were counted separately a) the number of polyps which were >4 mm; b) the number which were >3 mm; c)

the number which were ≥ 2 mm; d) if the preceding were <20, the number which were >1 mm was also counted; the size of all polyps of ≥ 6 mm was recorded separately. If sheets of nearly confluent polyps were present, an attempt was made to note the overall size of up to three such areas. The total number of polyps in each size category and estimated area of the lesions was then calculated by the biostastistician.

Reviewer's comment: The still photos used for colorectal polyp counting at baseline and 6-month follow-up exam have been submitted for FDA review. In addition, videotapes of baseline and follow-up colonoscopy and/or sigmoidoscopy have been submitted for FDA review as well.

Rectal biopsies: All polyps of ≥1 cm would be removed with cautery snare or cautery biopsy when possible. Decisions to proceed with initial drug treatment or continuation on study would be made by the committee of investigators, including the Principal Investigator and the colorectal surgeon, based on the number, size and pathology of such polyps, and on the completeness of the excision. These sites would be videotaped pre- and post-excision. Six biopsies of normal appearing mucosa (chosen under magnification in UT MD Anderson Cancer Center and after dye spray at St. Mark's) would be obtained from the rectum and the ascending colon (when present) for studies of crypt morphology, S-phase, M-phase and apoptotic cell fractions in isolated intact crypts and/or histologic sections. Three biopsies would be snap frozen for cyclooxygenase related studies. One biopsy of 2-4 polyps would be taken from immunohistochemical studies (e.g., apoptosis, p53). Two to six biopsies of polyps would be taken for cyclooxgenase studies and for –src and-yes. The biopsy priority order is crypt studies, immunohistochemistry, cyclooxygenase. At the six month endoscopy, up to 15 polyps would be biopsied if available (after the polyp scoring procedure is completed). In addition, one biopsy would be taken from up to four sites of presumably regressing polyps (such sites are described as pink halos) if found on follow-up endoscopies. These would be analyzed for crypt morphology and apoptotic index, p53, COX, mRNA/protein, and immunohistochemistry.

Colon: An attempt would be made to videotape each anatomic segment of the colon (ascending, transverse, descending, sigmoid and rectum, excluding the flexures) separately in a continuous clockwise spiral fashion. The designated regions for detailed and prolonged videotaping and scoring in all patients were: a) cecum b) the area between the ileocecal valve and 5 cm distally (indicated by endoscopic measuring instrument); c) the proximal transverse colon between the first and third folds distal to the hepatic flexure (distance indicated with the endoscopic measure); d) the

area between 20 cm from the anal verge and the rectum, and e) the rectum between the anal verge and the third valve of Houston.

In patients with an intact colon, the tattoo and still photography procedures were repeated in one or two areas in the proximal colon or in the transverse colon where polyp burden was high. The same procedure (five photographs) was performed in the cecum with the appendiceal orifice serving as the center instead of the tattoo. Three additional photographs were taken distal to the ileocecal valve, placing the valve at the side, bottom, and top of the field, respectively. Biopsies were not taken within the photographed areas of the colon.

The protocol on rectal biopsy above would be repeated in the transverse colon in patients with an intact colon, or from other sites of sufficient polyp burden. The same colonic segment would be biopsied on baseline and follow-up examination.

Duodenal Evaluation:

A sideviewing endoscope was used for examination of duodenal polyps. The duodenum was videotaped from the distal second part of the duodenum to the pylorus in a spiral fashion, and special attention was given to the second duodenal segment with the goal of leaving adequate evaluable polyps. The site and number of polyps seen and the size of the largest polyps were recorded and they were biopsied if >10 mm diameter each (polyp <10 mm were not biopsied, unless they numbered >10). The endoscopy form was completed with histologic data regarding polyp architecture and degree of dysplasia and a score and grade (0 or 1-4) is assigned. **Still photography, as described for the colon, was performed, with the papilla placed at the center and at each of the four mid-edges of the field. Still photography was also taken of each polyp of ≥ 10 mm.** Those polyps were also noted by voice on the audio-video tape to indicate the location. Photographs were taken with the open biopsy forceps against the mucosa. When the polyp burden was small, one photograph was taken with the closed biopsy forceps, 2 mm, near the smallest evaluable polyp, and one photograph with the open biopsy forceps, 6 mm near the largest polyp.

Reviewer's comment: The percent change in plaque-like areas in duodenum is the secondary efficacy endpoint. However, the method used to assess and quantify the plaque-like areas in duodenum was not prospectively defined in the original protocol. No photographs of plaque-like areas in duodenum were submitted for FDA review.

Duodenal biopsies: Polyps>1 cm in size will be biopsied for histopathology. The three largest polyps would be biopsied for immunochemical studies and for cyclooxygenase studies, provided that enough polyps remain for follow-up assessment

Spigelman Criteria

A standardized procedure for scoring duodenal polyps based on number, size, architecture, and histology that was developed at the St. Mark's Registry, the Spigelman Criteria, was applied to the data obtained from duodenal endoscopy. Four parameters, each categorized with predetermined qualitative or quantitative descriptors, were assessed. The parameters, and their respective categories, were: histology (normal, tubular polyp/hyperplasia/inflammation, tubulovillous, or villous); dysplasia (normal, mild, moderate, severe, or not evaluated); size of polyps (0, 1-4 mm, 5-10 mm, or >10 mm); and number of polyps (0, 1-4, 5-20, or >20). Baseline and end of study data were recorded on CRF No. 59.01. Spigelman grades were based on a 12-point scale and assigned as follows: 0 points corresponds to Grade 0; 1 to 4 points correspond to Grade I; 5 to 6 points correspond to Grade II; 7 to 8 points correspond to Grade III; and 9 to 12 points correspond to Grade IV. Each of the categories within each parameter had an associated score, ranging from 0 to 3, with the higher scores assigned to clinically worse conditions. The individual scores for each of the four parameters were summed and the corresponding Spigelman grade was assigned. Appendix 2.13 provides additional information regarding the CRFs on which efficacy data were recorded and describes relevant calculations.

Gastric and duodenal bulb Evaluations

Photographs were taken: a) from the gastro-esophageal junction towards the antrum; b) antrum, including the pylorus, c) retroflex view of the fundus, d) duodenal bulb, from the pylorus, e) three areas with the highest polyp burden; f) all ulcers ≥5 mm; g) three areas of most significant abnormalities, in patients with erosions, or two areas with the most significant abnormalities in patients without erosions. The latter photographs (items e-g) containing polyps, ulcers or erosions would include the open biopsy forceps.

Scoring mucosa integrity of the stomach and duodenal bulb: paired sets of coded photographs were scored for significant differences (estimate of 40-

50% difference) in the total burden of ulcers and erosions by the criteria of : a) significantly better; b) worse, or c) same.

Committee Review of Videotapes

In the original protocol, a committee comprised of Drs. Lynch and Steinbach, Williams, Phillips and an investigator from a non-participating center would meet at 5, 11, and 17 months of study initiation or more frequently if needed, to standardize the polyp measurement/videotape scoring methodologies and to review all the study videotapes and still photos in coded pairs (same patient at two time points with the corresponding photos in random order). **The quantitative polyp measurements and videoendoscopic scoring done at these sessions would be used for the final statistical evaluations. Preliminary measurements/scoring would be made by two investigators at each institution bimonthly. These would allow for interval statistical evaluations, and more important, for quality control, refinement, and further standardization of the techniques.**

Protocol Amendment No. 2 (January 21, 1997) **deleted the requirement that Committee members review the "cloverleaf" pictures to derive the primary efficacy endpoint. Committee members were only required to perform a global assessment** of each subject's baseline and follow-up videotapes (colorectal and duodenal) using a paired, random (with reference to their pre- or post-intervention status) sample and assigned a qualitative/semi-quantitative score. Scores were recorded according to "response", "non-response" or "progression". Additionally, estimates of the overall and regional percent change in polyp burdens were given for each pair of tapes without discussion as: better, worse or unchanged and estimate of percent of change for each location. Data were recorded on CRF Nos. 43, 50.01, 51.01 and 58, respectively. Appendix 2.13 provides additional information regarding the CRFs on which efficacy data were recorded and describes relevant calculations)

Committee review of Videotapes:

A committee comprised of five physicians (experienced endoscopists) provided an independent review of the endoscopy ***videotapes.*** Members of the committee, Drs. Lynch and Steinbach of MDACC, Phillips and Wallace of St. Mark's Hospital, and Rodriguez-Bigas (representing a non-participating polyposis center) met at both investigative sites on 8 September 1997 (UK), 5 January 1998 (UK), 6 April 1998 (US), 27 July 1998 (US) and 17-18 November 1998 (UK) to standardize the methodologies used to measure polyps and score videotapes.

The efficacy endpoints to be analyzed in this data set included:

- Percentage change from baseline in the number of colorectal polyps via composite "cloverleaf" photos
- Video assessment of global and regional colorectal polyp response: better, worse, or unchanged and estimate of percent change for each location
- Percent change in duodenal polyp status via composite "cloverleaf" photos (e.g., size, number, surface area)
- Video assessment of the duodenal polyp response

Investigational:

Patients at MD Anderson would also undergo examination of designated areas in the rectum and in the right colon, with a magnifying endoscope after coating the designated area with indigo carmine. Briefly, after applying indigo carmine, an area of grossly normal appearing mucosa was scanned with the magnifying endoscope and an area with high density of aberrant crypts was chosen where small India ink tattoos were made. A 6-mm rim, measured by the open biopsy forceps, around the tattoo were examined with the magnifying endoscope and videotaped. Four microscopic foci of both greatest and least density of aberrant crypts were photographed. These images would be assessed for the number and size of foci, number of crypts per focus, and architecture. Size would be estimated relative to normal crypts in the photograph. This pilot data would not be entered into the clinical and safety database.

Biopsies of normal appearing mucosa chosen under magnification at MD Anderson and after dye spray at St. Mark's would be obtained from the rectum and the ascending colon for investigational studies.

Gastric biopsies were taken for histology at the greater curvature aspect of the proximal body and proximal antrum, and at up to three other sites of representative pathology, at the discretion of the endoscopist. At St. Mark's Hospital, five gastric biopsies were snap frozen for genetic testing. In the duodenum, 12 polyps, when available, were removed with serial biopsies. Where possible, an attempt was made to completely excise those polyps with the biopsy procedure. Depending on the number of polyp samples available, approximately 20 biopsies of normal appearing mucosa were taken. The tissue samples were allocated for studies of cyclooxygenase isozyme expression, parameters of cell proliferation and apoptosis, deoxyribonucleic acid (DNA) adducts, and gene mutation. Polyps were biopsied for histopathology at the discretion of the

endoscopist. These pilot data were not entered into the clinical and safety databases.

6.1.8. Concomitant Medications

Adrenocorticosteroids, aspirin, or conventional NSAIDs should not be administered. If any of the above drugs were necessary for chronic use, the patient should be removed from the study.

6.1.9. Efficacy Assessment

The primary efficacy endpoint is the percentage change from baseline in the number of colorectal polyps.

The secondary endpoint is the percentage change in area of duodenal plaque-like polyps.

6.1.10. Safety Considerations

Adverse events were graded according to the NCI Common Toxicity Criteria. Adverse events not included in the NCI Common Toxicity Criteria were scored as follows: mild (grade 1: causing no limitation of usual activities), moderate (grade 2: causing some limitation of usual activities), grade 3-4 (causing inability to carry out usual activities) or death

An additional, unscheduled upper endoscopy could be performed at the discretion of the primary physician, and for the following indications:

- a decrease in Hgb $\geq$1.0 g/dL associated with gross upper intestinal bleeding or epigastric pain; or
- undiagnosed epigastric pain clinically attributable to ulcer disease, persistent for $\geq$2 weeks.

New onset of dyspepsia or reflux-related symptoms could be treated with antacids, or with H2-receptor antagonists (ranitidine, famotidine, cimetidine, nizatidine) for up to two weeks per incident. Patients requiring more prolonged treatment would need required upper endoscopy. Patients taking antacids or H2-receptor antagonists at entry were allowed to continue at their prestudy schedule.

All randomized patients who received at least one dose of study medication were included in the analysis of safety. All inferential statistical tests of safety data used two-sided tests with alpha at 0.05. Changes in weight and vital signs from baseline to Final Visit (Month 6 or Early Termination) were calculated and compared across treatment groups using one-way analysis of variance (ANOVA) and pair-wise comparisons with contrast statements.

Clinical laboratory data were summarized and compared between treatment groups using one-way ANOVA tests applied to change from the baseline to Month 1, Month 3, Month 6 and Final Visit for continuous variables and Fisher's exact test for categorical variables. Scatterplots were used to graphically depict the results. For evaluation of laboratory results, upper and lower limits representing values of potential clinical relevance were determined as were cutoff values considered to represent lower and upper extremes. These upper and lower mid-range and extreme values were developed following discussion with external safety consultants. Shift tables were constructed using these cutpoints. The cutpoints are shown on each individual shift table.

6.1.11. Statistical Plans

The statistical analysis plan, originally developed 18 August 1998, was amended on 8 December 1998 to incorporate changes agreed upon in discussion with FDA. **This amendment was finalized prior to breaking the blind for statistical analyses.**

Patient Populations Analyzed

The Intent-To-Treat (ITT) analysis included all randomized patients who took at least one dose of study drug, and this is the analysis of major focus. Evaluable patients were defined as those meeting all of the following criteria:

- Had taken at least 80% of the study medication over the course of the study;
- Had taken at least 80% of the study medication during the last 60 days prior to the end-of-study endoscopy, with no more than six consecutive days off drug;
- Had endoscopies both at baseline and Month 5 or later; and,
- Had final endoscopy done within 14 days after stopping double-blind medication.

Demographic and Baseline Characteristics

Summary statistics for all randomized patients were tabulated by treatment group. The Kruskal-Wallis test was used to compare across the three treatment groups for the continuous variables (age, height, weight, vital signs, all colorectal variables, and the SF-36 Health Survey [country specific, standard]). Fisher's exact test was used for the categorical variables (race/ethnic origin, gender, and colon status).

Missing Data

Missing data rules, applicable to the primary and secondary endpoints, were those delineated in the Amendment to the Statistical Analysis Plan, dated 8 December 1998. For five discontinued patients with no data beyond baseline, all percent changes from baseline scores for the primary endpoint were to be defined as 0%. This allowed all five to be included in the intent-to-treat analysis.

As noted before, duodenal-only patients were not included in the analyses of the colorectal, colon or rectal efficacy variables.

Relative to the secondary endpoint, there were two patients with no duodenal plaque at baseline and some duodenal plaque at end of study. Since the percent change from baseline for these patients could not be determined, the baseline value of 1% was assigned both these patients. This allowed both patients to be included in the secondary endpoint analysis.

Sample size calculation: From the results of placebo-controlled studies involving FAP patients treated with the NSAID sulindac, the average percent change from baseline in the number of polyps was found to be either zero or close to zero in the placebo group. Furthermore in these studies, the average percent change from baseline in the number of polyps in the active treatment group was found to exceed 40%. Thus, fewer patients in this study would be randomized to the placebo group as compared to each of the two active treatment groups since it is anticipated that the patients in the placebo group would not experience any clinical improvement in their conditions. The standard deviation for the percent change from baseline in the number of polyps is not well defined. However, from the previous studies, the range of 20% to 40% for the standard deviation seems acceptable. Based on this range for the population standard deviation, and assuming that two centers would be used in this study, 15 patients in the placebo group and 30 patients in each active treatment group would provide more than 80% power to detect a maximum difference of at least 40% among the actual treatment means of the primary efficacy variable.

Patients would be replaced if they stop study drug for any reason other than toxicity or are not evaluable as defined above for reasons other than toxicity. Replacement patients would be assigned to the same treatment as the patients who had been dropped.

Interim analysis: Should the accrual rate become one or fewer patients per month for six consecutive months before 50% of the planned number of patients have been accrued, then two analyses, interim and final, of the comparative efficacy and safety would be undertaken. The interim analysis would be performed on the primary efficacy variable. The Lan-DeMets alpha spending procedure would be used to make adjustment to the nominal p-value (0.05) to account for the interim analysis. The p-values to be used were 0.0005 and 0.0495 at the interim and final looks respectively. The blind would be broken for the interim analysis on a treatment group basis only. Individual patient treatment assignments would not be identified and the results of the interim analysis would be reported only to individuals within Searle and NCI.

Primary Efficacy Variable

The primary analysis was that of the single primary endpoint, the percent change from baseline in the number of colorectal polyps for all ITT patients. Treatment efficacy was based on comparison of high dose (400 mg BID) versus placebo and low dose (100 mg BID) versus placebo. These comparisons were based on type I errors of 0.04 and 0.01, respectively. Allocation of significance levels was based on an agreement with the FDA (see Amendment to the Statistical Analysis Plan, dated 8 December 1998).

Analyses of all continuous outcome measures were performed using an analysis of variance (ANOVA) model with terms for center, treatment, and treatment by center interaction. When the overall treatment comparison is significant, pairwise comparison of the treatment groups was carried out using the Fisher's Least Significant Difference (LSD). A supplementary analysis of covariance was performed to adjust for age, sex, surgical status and NSAID use status. Discrete or categorical outcome measures were analyzed using the Cochran-Mantel-Haenszel (CMH) test controlling for study center. All statistical tests were two-sided. In addition, except for safety comparisons, all efficacy comparisons would use a significance level of 0.10. The two-sample Wilcoxon nonparametric test was used to compare each of the two CELEBREX treatment groups with the placebo group.

<u>Additional Requests Made by the FDA</u>

As suggested by the FDA at the pre-Supplemental New Drug Application (sNDA) meeting, held March 29, 1999, a cumulative distribution function for the primary efficacy endpoint for each treatment group is provided.

Colon and Rectal Polyps

The number of colon and/or rectal polyps was computed by adding the number of polyps (from "cloverleaf" still photographs) across the size categories to obtain one number at each of the two time points to assess pertinent variables. Patients with no rectum were not eligible for analysis of rectal-only variables. Colorectal polyp size calculations were done by assigning the values of 2.5 mm, 3.5 mm, and 4.5 mm to size categories of 2-3 mm, 3-4 mm, and 4-5 mm, respectively. The actual size (mm) was used for colorectal polyps >5 mm. A mean colorectal polyp size was computed for each patient at each of the two time points, and the percent change from baseline was computed. The two-sample-Wilcoxon nonparametric test was used to compare the two CELEBREX treatment groups with the placebo group using percent change as the dependent variable and treatment as the independent variable. These tests were computed using both the ITT and the Evaluable Groups. Appendix 2.13 provides additional information regarding the CRFs on which efficacy data were recorded and describes relevant calculations.

Secondary Efficacy Variable

The single secondary endpoint was the percent change from baseline in area of duodenal plaque-like polyps. The key statistical treatment comparisons and the corresponding type I errors were the same as those used for the primary endpoint. The mean percent area of the duodenum covered by plaque-like polyps was computed across two duodenal photographs, one high polyp density photograph and one low polyp density photograph. Mean percent areas were obtained at baseline and at Month 6/Termination. The two-sample Wilcoxon nonparametric test was used to compare each CELEBREX treatment group versus the placebo group.

Tertiary Efficacy Variables

- The percent change in the number of colon polyps for patients with at least five such polyps at baseline.
- The percent change in the number of rectal polyps for patients with at least five such polyps at baseline.
- The percent change in the number of rectal polyps for patients with at least five such polyps at baseline based on high density and low density photographs.
- The percent change in the mean size and total size of colorectal polyps.
- The percent change in the number of non plaque-like duodenal polyps for patients with at least five such polyps at baseline.
- The percent change in the area of the duodenal ampulla.

- Change in the Spigelman grades for the duodenum.
- Physicians' assessment of change in duodenum based on blinded review of corresponding videotapes.
- Physicians' assessment of change in rectum and colon based on blinded review of corresponding videotapes.

Duodenal Ampulla

The product of the two greatest diameters of the duodenal ampulla was computed for each patient at each of the two time points, and the percent change from baseline was obtained using these two products. Appendix 2.13 provides additional information regarding the CRFs on which efficacy data were recorded and describes relevant calculations.

Spigelman Grade

The number of patients with each Spigelman grade at baseline and Month 6/Termination was summarized, as was the number of patients with changes in Spigelman grades (-4 to + 4) from baseline to Month 6/Termination. Four parameters (histology, dysplasia, size and number of polyps), each categorized with predetermined qualitative or quantitative descriptors, were assessed. Spigelman grades were based on a 12-point scale and assigned as follows: 0 points corresponds to Grade 0; 1 to 4 points correspond to Grade I; 5 to 6 points correspond to Grade II; 7 to 8 points correspond to Grade III; and 9 to 12 points correspond to Grade IV. Each of the categories within each parameter had an associated score, ranging from 0 to 3, with the higher scores assigned to clinically worse conditions. The individual scores for each of the four parameters were summed and the corresponding Spigelman grade was assigned. Decreases and increases in Spigelman grades were indicative of improvement and worsening, respectively. If any of the component parameters of the Spigelman grading was missing, the overall Spigelman grade was recorded as missing, and missing data were not imputed. Due to a large number of cells with zero patients, the Spigelman scores were collapsed into improved, no change, and worsened for the Cochran-Mantel-Haenszel (CMH) tests. Three distinct CMH tests for pairwise treatment comparisons were applied to these data. Appendix 2.13 provides additional information regarding the CRFs on which efficacy data were recorded and describes relevant calculations.

Discrete Duodenal Polyps

The percent change in the number of duodenal non-plaque-like polyps could not be analyzed. Only twelve patients had duodenal non-plaque-like polyps at baseline and none met the requirement for at least five such polyps.

Physician Assessment

Each physician examiner viewed the Baseline and Month 6 (or termination) videos in a blinded fashion, and made an assessment of either improved, the same, or worsened. Numerical scores of 1, 0 or -1, respectively, were assigned to the assessments in order to compare the two time points. The mean of the five raters' assessments was calculated for each video comparison (one for the rectum, two for the colon, and one for the duodenum). A video comparison marked as "unreadable" (usually in situations where the respective gastrointestinal tract segment had been surgically removed or due to videotape equipment failure) was treated as missing data, and no imputation was done for missing videotape data. The two-sample Wilcoxon nonparametric test was applied to the video assessments with mean score as the dependent variable and treatment as the independent variable. Although the CMH procedure was specified in the original statistical analysis plan, the two-sample Wilcoxon test was used. The primary comparison was 400 mg BID versus placebo. Comparison of 100 mg BID versus placebo and 100 mg BID versus 400 mg BID was considered secondary or exploratory. These tests were done for both the ITT and Evaluable Groups. Appendix 2.13 provides additional information regarding the CRFs on which efficacy data were recorded and describes relevant calculations.

Quality of Life Assessments

Distinct questionnaires validated for the UK and the US were employed at the respective investigative sites. Scores of eight domains for the SF-36 Health Survey (country specific, standard) were calculated. The eight domains included: Physical Functioning, Role-Physical, Bodily Health, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health. The scores for the US version were calculated using the methods found in How to Score the SF-36 Health Survey (17). The scores for the UK version were calculated using the methods found in the SF-36 Health Survey Scoring Manual for English Language Adaptations (18). Certain items were recorded so that a higher item value indicated better health status on all items. Each of the eight domain scores was composed of multiple items. If the patient left one or more questionnaire items in a domain blank, and had answered at least 50% of the items that made up a domain score, then the average score, across completed items in the same domain, was used in place of the missing item. Raw domain scores were then computed by summing across items in the same domain. A linear transformation was applied to the raw scores to produce a scale ranging from 0 to 100 for each domain, with a higher numerical score corresponding to a greater patient quality of life. The changes from baseline to endpoint scores were analyzed for each domain using the two-sample Wilcoxon Rank Sum test.

Dose Response

Dose response for key continuous efficacy variables was based on the nonparametric Jonckherere-Terpstra test. Dependent variables included the percent change in the number of colorectal polyps, percent change in the number of rectal polyps, percent change in mean colorectal polyp size, and the change from baseline in the percent area of the duodenum covered with plaque-like polyps.

6.2. *Pivotal trial results*

Patients were eligible to participate in the study if they had a diagnosis of FAP by clinical history/family history or genetic testing. Patients with molecular diagnosis of FAP must have ≥2 adenomas in order to be eligible. Seventy-seven patients had an endoscopically assessable colonic and/or rectal segment, and an additional six patients had duodenal polyps but no evaluable colorectum. If a patient had used any non-steroidal anti-inflammatory drug (NSAID), including aspirin, at any dose at a frequency averaging ≥3 times per week during the six months before study entry, a six-month washout period was required. Use of any dose of an NSAID at an average frequency of one to two times per week during the six months before study entry required a three-month washout period.

Reviewer's comments: Pilot studies, which included biomarker studies (aberrant crypt foci, crypt morphology, COX-1 and COX-2 levels, tissue eicosanoid levels, measures of proliferation and apoptosis) as well as a food intake study were conducted but not submitted in this supplemental NDA. Family history assessment and pedigree worksheets were obtained during baseline evaluation but not submitted in this supplemental NDA.

1.1.1. Study execution

Eighty-three patients were randomized in the study and received at least one dose of study drug.

Ineligible patient:

One patient (50230032) on 100 mg BID was ineligible due to a history of allergy to NSAID

Protocol violations:

8 patients had abnormal laboratory tests prior to randomization (2 on placebo, 3 on 100 mg BID, and 3 on 400 mg BID)

2 patients on 100 mg BID had a positive pregnancy test within 14 days prior to randomization

The applicant reported that 9 patients deviated from the protocol regarding their use of prohibited concomitant medications. Of these 9 patients, 7 patients deviated from the protocol by their intermittent use of NSAIDs (1 in the placebo group, 2 in the 100 mg BID group and 4 in the 400 mg BID group). The remaining 2 patients deviated from the protocol by their intermittent use of corticosteroids.

Reviewer's comments: The use of NSAIDs in these patients is less than one week except one patient who used NSAID for 185 days. However, according to the database, this patient only took a total of 8 tablets during the 185 days. Therefore, the use of NSAIDs in these patients is unlikely to have a significant effect on the efficacy endpoints of this study.

Missing procedures or assessments:

1 patient (50490067) with an intact colon had baseline sigmoidoscopy and colonoscopy but no photos exist.

4 patients (3 on 100 mg BID and 1 on 400 mg BID) did not have lower GI endoscopy at the 6-month follow-up.

6 patients (1 on placebo, 1 on 100 mg BID and 4 on 400 mg BID) had no baseline assessments on duodenal plaques or incomplete baseline assessments on duodenal plaques.

6 patients (3 on 100 mg BID and 3 on 400 mg BID) did not have assessments of duodenal plaques at 6-month follow-up exam.

Patient disposition:

Table 5: Patient disposition

	Placebo (N=17)	100 mg BID (N=34)	400 mg BID (N=32)
Follow-up days median (range)	248 (203-422)	246 (90-439)	247 (126-474)
Number of patients who completed study	17	31	30
Number of patients who dropped out Reason for dropout	0	3 suicide lost to f/u noncompliance	2 allergy (gr 3) indigestion (gr 2)

Patient compliance:

Compliance with medication was assessed by pill counting. 74 patients missed at least one dose of the study medication.

Table 6: Patient compliance

Number of patients	Placebo (N=17)	100 mg BID (N=34)	400 mg BID (N=32)
Took ≥80% of study medications	17	30	28
Took ≥80% of study medications for 60 days before end of study	16	28	28
Missed ≥1 dose	16	28	30
Number of missed doses median (range)	11 (1-55)	12 (1-55)	10 (1-107)

The following two scatter plots (Figure 2 and Figure 3) attempted to correlate the number of missed doses with the percent change in the number of colorectal polyp counts:

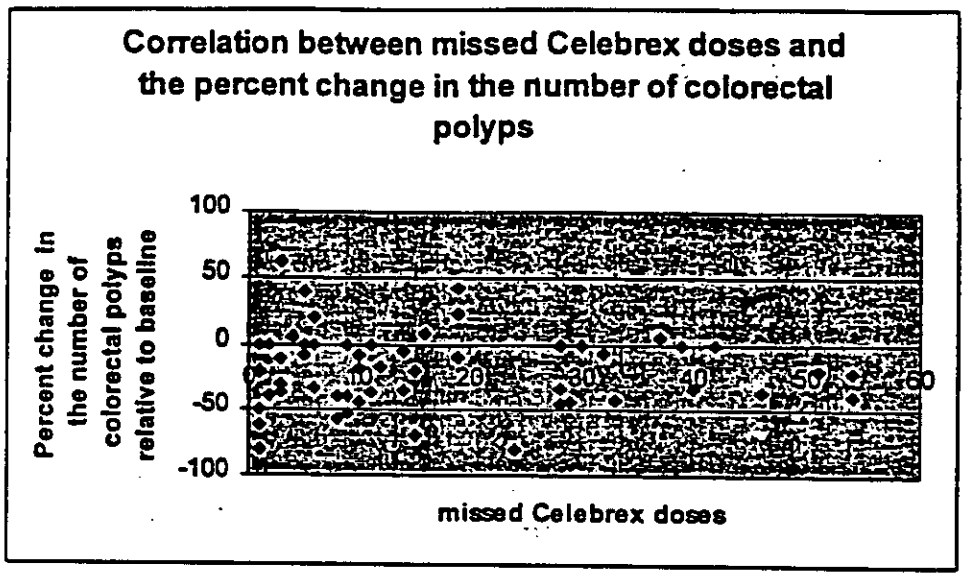

Figure2: Correlation between missed Celebrex doses and the percent change in the number of polyps (relative to baseline) in patients who were on 100 mg BID or 400 mg BID

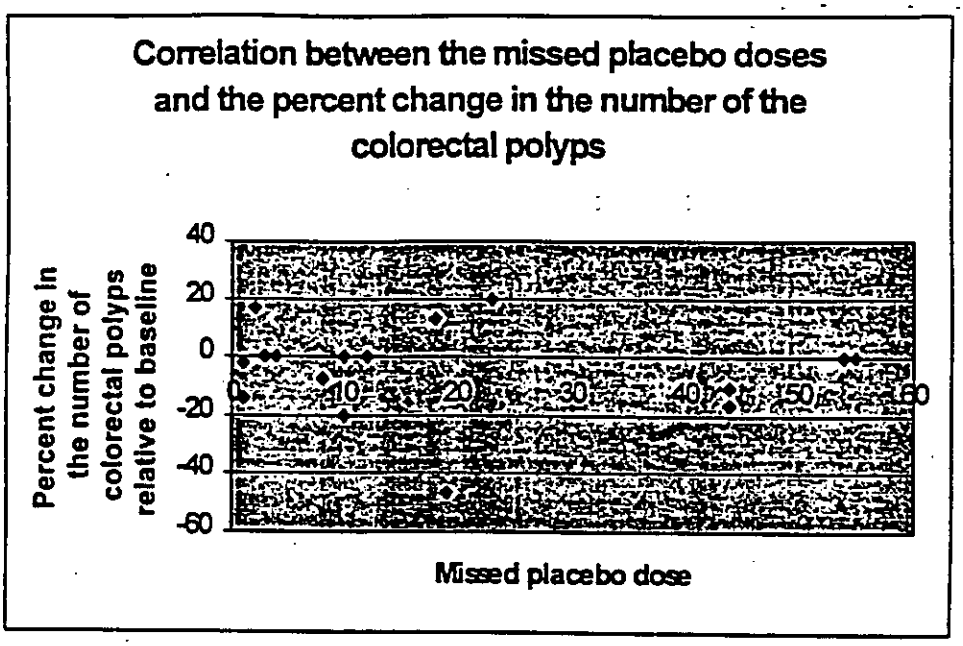

Figure3: Correlation between missed placebo doses and the percent change in the number of polyps (relative to baseline) in patients who were on placebo

Reviewer's comment: The above two scatter plots did not reveal any obvious correlation between the missed Celebrex doses or placebo doses and the percent change in the number of the colorectal polyps relative to baseline.

6.1.2. Baseline characteristics

The applicant reported that all treatment groups were similar with respect to height, weight, colon status, and vital signs at baseline, however, the groups were statistically different (p=0.013) for age at baseline, with the placebo group being oldest (41.2 years), the CELEBREX 100 mg BID group being slightly younger (39.5 years) and the CELEBREX 400 mg BID group being youngest (33.0 years).

FDA analysis showed a difference in the median age among the three groups. In addition, the median time (months) since colectomy was longest in placebo group, followed by 100 mg BID group and then 400 mg BID group. Compared with 5/17 patients (29%) on placebo and 8/34 (24%) on 100 mg BID, 12/32 patients (48%) in the 400 mg BID group had intact colon.

Table 7: Patient demographics

	Placebo (N=17)	100 mg BID (N=34)	400 mg BID (N=32)
Age Median Range	40 20-64	39 19-56	31 20-60
Number of patients with intact colon and rectum Age <=20 >20-<=30 >30-<=40 >40	5 1 0 2 2	8 3 0 3 2	12 1 7 2 2
Number of patients with subtotal colectomy (ileorectal anastomosis)	10	25	18
Number of patients with total colectomy (ileoanal anastomosis) Months since total colectomy	2 142, 219	1 184	2 39, 150
Months since subtotal colectomy Median range	N=10 179 150-447	N=24* 166 23-474	N=18 103 16-230

*One patient with subtotal colectomy did not have colectomy date in the database

62 patients had assessable rectal polyps at baseline (11 on placebo, 28 on 100 mg, 23 on 400 mg). 21 patients had no assessable rectal polyps (6 on placebo, 6 on 100 mg, and 9 on 400 mg). Out of these 21 patients, 15 have assessable colonic polyps (4 on placebo, 4 on 100 mg, and 7 on 400 mg). 6 patients had duodenal only disease (2 on placebo, 2 on 100 mg, and 2 on 400 mg).

Table 8: Colorectal polyp burden in tattoo or marked area(s)

Polyp burden	Number of patients who had the specified range of polyps		
	Placebo	100 mg BID	400 mg BID
Number of rectal polyps in tattoo area			
0	2	2	3
1-9	6	19	19
10-19	4	9	6
20-29	0	2	1
>=30	3	0	1
Number of colonic polyps in marked areas			
0	0	1	0
1-9	2	4	6
10-19	3	1	6
20-29	0	2	0
>=30	0	0	0

70 out of 83 (84%) patients had APC gene tests with results. 9 out of these 70 patients tested positive for attenuated FAP by genotype. 7 out of 9 patients who tested positive for attenuated genotype had phenotype attenuated FAP. There were 4 patients who had attenuated FAP by phenotype only.

Table 9: Number of patients who had APC gene test and had attenuated APC

	Placebo (N=17)	100 mg BID (N=34)	400 mg BID (N=32)
APC gene test			
Done with results	15	28	27
Not done	1	1	1
Done, cannot find results	1	5	4
APC gene test results			
Phenotype attenuated APC	2	3	8
Attenuated genotype	2	3	4

Reviewer's comments: The codes for the variables in the genetic dataset need to be clarified. The applicant did not provide the dataset on family history and pedigree. 80 out of 82 patients had dietary assessment at baseline but dataset on dietary assessment was not submitted in this sNDA.

6.1.3. Efficacy results

The primary efficacy variable was the percent change from baseline in the number of colorectal polyps for patients with five or more such polyps at baseline (excluding the patients with duodenal polyps only). The secondary efficacy variable was the percent change from baseline in the area of the duodenum covered by plaque-like polyps.

- Applicant's analysis: Compared to placebo, CELEBREX 400 mg BID for 6 months significantly reduced the number of colorectal polyps by 28.0% ($p=0.003$). The robustness of this finding was supported by a significantly increased ($p=0.003$ vs. placebo) percentage of responders (defined as patients with $\geq$25% reduction in the number of colorectal polyps), a 4.9% reduction in mean residual colorectal polyp size ($p=0.055$ vs. placebo), a 30.7% reduction in colorectal polyp burden ($p=0.001$ vs. placebo), a 30.8% reduction in the number of colon polyps and a 24.3% reduction in the number of rectal polyps. In addition, there was a reduction in number and percent of patients in the CELEBREX 400 mg BID group (2 of 30 patients, 7%) compared to the placebo group (3 of 15 patients, 20%) who experienced an increase in the number of colorectal polyps. Physician review (blinded) of videotaped endoscopies of the colon and rectum demonstrated clinical benefit and confirmed these observations ($p\leq0.015$). The findings for the CELEBREX 100 mg BID treatment group also supported the trend for benefit.

  CELEBREX 400 mg BID for 6 months reduced the area of the duodenum covered by plaque-like polyps (dysplastic tissue) by 14.5%, but this reduction was not statistically significant compared to the change in the placebo group of 1.4% due to the high degree of variability in patient response. Supporting findings included a trend towards increased improvement relative to the placebo group based on the Spigelman Criteria. Physician review (blinded) of videotaped endoscopies of the duodenum indicated clinical benefit with the CELEBREX 400 mg BID group having significantly greater improvement than the placebo group ($p=0.033$).

  Patients in the CELEBREX 400 mg BID group had qualitatively higher health-related quality of life scores. However, the SF-36 Health Survey

(country specific, standard) did not show significant changes in health-related quality of life after 6 months of treatment with either dose of CELEBREX compared to placebo treatment.

- FDA analysis: FDA analysis of the primary efficacy endpoint using the applicant's dataset confirmed the applicant's results.

Table 10: FDA analysis of the primary efficacy endpoint based on applicant's dataset

Primary Efficacy	placebo	100 mg BID	400 mg BID
% ↓ in colorectal polyps			
Mean in ITT (Range)	-4.5 (N=15) (-46.7, 16.7)	-14.5 (N=33) (-100, 62)	-28 (N=30) (-80, 20)
p-value (when compared to placebo)		0.327	0.003
Mean in evaluable* (range)	-4.5 (N=15) (-46.7, 16.7)	-16 (N=30) (-100, 62)	-28 (N=29) (-80, 20)

* excluding 4 patients with no follow-up sigmoidoscopy or colonoscopy

We performed covariate analyses using ANOVA model. The covariates used are patient age (either as a continuous variable or a binary variable i.e., >30 years or not), time since subtotal colectomy (either as a continuous variable or a binary variable i.e. <5 years or not), colon status (intact colon or not), attenuated FAP phenotype (yes or no). None of the above covariates are significant predictors of the primary efficacy variable for this data set. The models included all of the covariates, each covariate separately, and other combinations. In all cases, the difference between the primary efficacy variable in the placebo and 400 mg arms was significant at p=0.05 after adjusting for the other covariates. Also, none of the covariates was significant even at the 0.2 level.

Reviewer's comment: The applicant's primary efficacy endpoint i.e., the percent change in the number of colorectal polyps relative to baseline was derived from still photographs. Rectal polyp count was based on still photos with a tattoo in the center. Colonic polyp count was based on one or two still photos with a tattoo in the center and two still photos with anatomic markers of either ileocecal valve or appendiceal orifice. Dr. Wallace from St. Mark's Hospital in London did the colorectal polyp counts on all patients at St. Mark's Hospital and MD Anderson Cancer Center. There is no INDEPENDENT confirmation of the primary efficacy endpoint, as determined by Dr. Wallace, by another investigator or a review committee.

FDA staff including a gastroenterologist with expertise in endoscopy has met with Dr. Wallace to learn the methodology used in polyp counting. FDA review of the still photographs has revealed the following problems:

- The still photographs from MD Anderson Cancer Center submitted on June 25, 1999 are NOT photographs but are prints from a color printer and are of inferior quality when compared to photographs from St. Mark"s. Still photographs were submitted on December 3, 1999.
- Multiple photographs were submitted for one tattoo or anatomically marked area and it was not possible to determine which ones were used to derive the colorectal polyp count in the primary efficacy dataset..
- According to the protocol and manual submitted in the sNDA, only one still photo i.e., either tattoo center or an anatomically marked area should be used to count the polyps. The sponsor stated only the "best" photograph was used for polyp counting. The "best" photograph used by Dr. Wallace for polyp counting was not specifically labeled. Dr. Steinbach from MD Anderson agreed that polyp counting would be different depending on the photograph(s) used.
- Often the final photographs of the same areas are not comparable to the baseline photographs in orientation, lighting, etc
- During our session with Dr. Steinbach on December 9, 1999, we were told by Dr. Steinbach that a video counting of polyps at tattoo and anatomically marked area(s) was done under his supervision at MD Anderson. The video counting was performed on all patients at MD Anderson and St. Mark's. According to Dr. Steinback, the primary efficacy endpoint by video counting was very similar to that by still photograph counting. Specifically, there was a mean 30% reduction in colorectal polyp counts in the 400 mg group.

Blinded to the treatment assignments, FDA performed polyp counts on 28 patients from St. Mark's. FDA counts on the 400 mg BID group were very similar to the applicant's.

Table 11: Efficacy results on 28 patients from St. Mark's

Mean percent change in polyp count	FDA	Applicant
Placebo (N=4)	+15%	-11%
100 mg (N=11)	+85.3%	-2.2%
400 mg (N=13)	-32.6%	-33.3%

Searle submitted information on the video counting on December 16, 1999 as requested by FDA. Searle confirmed that video counting of colorectal polyps in tattoo and marked area(s) were performed on 77 patients who had colorectal segments. Six patients had either missing baseline or missing final videos. The percent change values for these six patients were imputed to be 0%. The colorectal endoscopic videotapes were used to count the number of polyps extended sites that included the tattoos and anatomic landmarks (ileocecal valve,appendix, and rectum) as references. Consecutive still frames of the videotapes, including all scored (i.e., counted) polyps were captured on the Olympus Image Manager computer program and each scored polyp was labeled and assigned a consecutive number. All polyps in a designated area (e.g., rectum) were counted as part of this assessment. Dr. Fujimura at MD Anderson scored all the colorectal endoscopic videotapes under the supervision of Dr. Steinbach. In addition, Dr. Steinbach reviewed random scores for accuracy and confirmed the polyp counts obtained by Dr. Fujimura. All scoring was done in a fully blinded manner i.e. the person who did the counting was blinded to the treatment assignments and the timing of the videotapes (baseline vs. final). Using the same method, Dr. Wakabayashi at MD Anderson separately counted the polyps in a subset of 24 patients and the results were in agreement with those of Dr. Fujimura.

Table 12: Percent change in colorectal polyp by video counting as per Searle

Percent change in polyp number (%)	Placebo N=15	100 mg BID N=32	400 mg BID N=30
All patients			
Mean	-10.0	-3.7	-29.0
SD	18.8	48.0	33.5
P value by wilcoxan rank sum when compared to placebo		0.765	0.033
MD Anderson Site (N=36)			
Mean	-1.2	-15.2	-26.3
SD	15.6	28.2	39.6
P value by wilcoxan rank sum when compared to placebo		0.223	0.077
St. Mark's site (N=40)			
Mean	-17.7	6.4	-31.4
SD	18.8	59.5	29.7
P value by wilcoxan rank sum when compared to placebo		0.662	0.270

According to Searle, the correlation between the percent change in colorectal polyps based on Dr. Wallace's counts and the percent change in colorectal polyps based on Dr. Fujimura's is statistically significant (p=0.004 for Pearson correlation, p=0.006 for Spearman rank correlation).

Searle submitted a SAS transport file containing the percent change of colorectal polyps in tattoo and anatomically marked area(s) by video counting on 12/20/99. Five patients who had no colorectal segments were excluded from the analysis. Four patients had no follow-up video and the percent changes in these four patients were imputed as 0%. No percent change by video counting was available in three patients and the reason for missing data was not clear from the submission by Searle. The percent changes in these three patients were also imputed as 0%. FDA analysis confirmed the mean percent change in polyp count in each treatment group as in table 12.

We performed covariate analysis using ANOVA model. The covariates are patient age (either as a continuous variable or a binary variable i.e., >30 years or not), time since subtotal colectomy (either as a continuous variable or a binary variable i.e. <5 years or not), colon status (intact colon or not), attenuated FAP phenotype (yes or no). None of the above covariates are significant predictors of the primary efficacy variable for this data set. The models included all of the covariates, each covariate separately, and other

combinations. In all cases, the difference between the primary efficacy variable in the placebo and 400 mg arms was significant at p=0.05 after adjusting for the other covariates.

FDA analysis of the correlation between the percent change in colorectal polyps based on Dr. Wallace's counts and the percent change in colorectal polyps based on Dr. Fujimura's showed a fair correlation with $\rho = 0.292$ (Pearson's product moment correlation, p-value=0.01). The scatter plot was shown in figure 4.

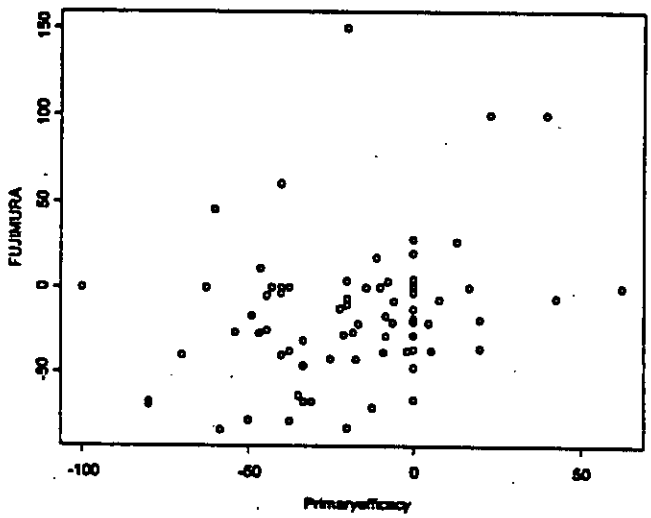

Figure4: Scatter plot of the percent change measured by two different methods (photograph or video).

FDA analysis of the secondary endpoint is based on the applicant's dataset. No still photos on duodenal plaques were submitted for FDA review. Therefore, FDA cannot verify the secondary endpoint. Four patients (2 on 100 mg BID and 2 on 400 mg BID) had no baseline assessments of duodenal plaques. In addition, three patients (1 on 100 mg BID and 2 on 400 mg BID) did not have assessments of duodenal plaques at follow-up exam. These 7 patients were not included in the FDA analysis. 29 patients had no duodenal plaques at baseline (5 on placebo, 11 on 100 mg BID, and 13 on 400 mg BID). 2 out of these 29 patients (both on 100 mg BID) developed duodenal plaques at the 6-month follow-up exam. Baseline percent area of duodenal was assigned 1% in these 2 patients. The remaining 27 patients were not included in the FDA analysis. Therefore, 49 patients (12 on placebo, 22 on 100 mg BID

and 15 on 400 mg BID) were in the FDA analysis of the secondary efficacy endpoint.

Table 13: Secondary efficacy endpoint

Secondary Efficacy	Placebo (N=12)	100 mg BID (N=22)	400 mg BID (N=15)
Mean % ↓ in percent area of plaques			
Applicant:	-1.4	110	-14.5 (p=0.36)
FDA	-1.4	123.3	-16.5 (p=0.402)

6.1.4. Safety results

The applicant reported that similar numbers and types of adverse events were observed in equivalent proportions of patients across all treatment groups. The most commonly reported adverse events included diarrhea, dyspepsia, fatigue, blood per rectum, upper respiratory tract infection and rash. There were no significant increases in incidence for any adverse event in CELEBREX treatment groups. The incidence of GI-related adverse events was also similar across treatment groups (71%-84%) with diarrhea being the most frequent (reported by 32%-44% of patients). The blood per rectum (rectal spotting) findings reported for all treatment groups in this study were neither unexpected nor clinically significant. The types of side effects seen in this study are similar to those observed in the arthritis studies. Intestinal surgical anastomotic ulceration was the only adverse event reported by CELEBREX-treated patients in the FAP trial that was not reported in the arthritis studies. This was only observed in 3 of 58 patients who had prior intestinal surgery before entering the FAP study.

Three patients withdrew from the study due to an adverse event as follows: 1 (3%) patient in the CELEBREX 100 mg BID group (suicide) and 2 (6%) patients in the CELEBREX 400 mg BID group (allergic reaction and dyspepsia). Three patients reported serious treatment-emergent adverse events as follows: 2 (6%) CELEBREX 100 mg BID patients (suicide and elective resection of existing angiofibroma), and 1 (3%) CELEBREX 400 mg BID patient (allergic reaction). One CELEBREX 100 mg BID patient committed suicide while taking study drug and one CELEBREX 400 mg BID patient committed suicide after being off study drug for 122 days. Neither of these events was considered related to study drug. There were no consistent alterations in mean laboratory test values.

FDA's analysis of safety data was based on the adverse event dataset submitted by the applicant.

Table 14: Number of patients who experienced at least one of the listed toxicities

Toxicity	Placebo (N=17)	100 mg BID (N=34)	400 mg BID (N=32)
Grade 2	11	16	15
GI	6	10	11
Nausea		4	1
Vomiting	1	1	1
Diarrhea	2	7	5
Abd pain	2		2
indigestion			1
Pancreatitis	1		
Bld in stool	1		1
Rectal pain	1		
Rectal burning			1
Grade 3	1 lymphoma	3 suicide diarrhea/abd pain angiofibroma	2 allergy incisional pain

One patient on 100 mg BID committed suicide after 90 days on study. The suicide occurred fifteen days after the patient dropped out of the study. The reason for dropping out of the study was unclear and there were no documented adverse events in the database.

One patient on 100 mg BID and two patients on 400 mg BID developed mild ulcerations at the ileal anastomotic sites.

6.1.5. Safety summary in arthritis patients

The recommended dosing regimen for FAP patients is 400 mg orally twice a day for six months. The longest duration of treatment for patients with osteoarthritis or rheumatoid arthritis is six months. The following is a summary of the applicant's analysis of safety data in arthritis patients treated with CELEBREX:

CELEBREX was evaluated for treatment of the signs and the symptoms of OA of the knee and hip in approximately 4,200 patients in placebo- and active-controlled clinical trials of up to 12 weeks duration. In patients with OA, treatment with CELEBREX 100 mg BID or 200 mg QD resulted in improvement in the WOMAC (Western Ontario and McMaster Universities) osteoarthritis index, a composite of pain, stiffness, and functional measures in OA. Doses of 200 mg BID provided no additional benefit above that seen with 100 mg BID.

CELEBREX was evaluated for treatment of the signs and symptoms of RA in approximately 2,100 patients in placebo- and active-controlled clinical trials of up to 24 weeks in duration. CELEBREX was shown to be superior to placebo in these studies, using the ACR20 Responder Index, a composite of clinical, laboratory, and functional measures in RA. Although CELEBREX doses of 100 mg BID and 200 mg BID were similar in effectiveness, some patients derived additional benefit from the 200 mg BID dose. Doses of 400 mg BID provided no additional benefit above that seen with 100-200 mg BID.

More than 8,500 patients have received a total daily dose of CELEBREX of 200 mg (100 mg BID or 200 mg QD) or more, including more than 400 treated at 800 mg (400 mg BID). Approximately 3,900 patients have received CELEBREX at these doses for 6 months or more; approximately 2,300 of these have received it for 1 year or more and 124 of these have received it for 2 years or more.

Table 13 lists all adverse events, regardless of causality, occurring in ≥2% of patients receiving CELEBREX from 12 controlled studies conducted in patients with OA or RA that included a placebo and/or a positive control group.

Table 15
Adverse Events occurring in ≥2% Of Celebrex Patients from Controlled Arthritis Trials

	Celebrex 100-200 mg BID or 200 mg QD (N=4146)	Placebo (N=1864)	Naproxen 500 mg BID (N=1366)	Ibuprofen 800 mg TID (N=387)	Diclofenac 75 mg BID (N=345)
Gastrointestinal					
Abdominal pain	4.1%	2.8%	7.7%	9.0%	9.0%
Diarrhea	5.6%	3.8%	5.3%	9.3%	5.8%
Dyspepsia	8.8%	6.2%	12.2%	10.9%	12.8%
Flatulence	2.2%	1.0%	3.6%	4.1%	3.5%
Nausea	3.5%	4.2%	6.0%	3.4%	6.7%
Body as a whole					
Back Pain	2.8%	3.6%	2.2%	2.6%	0.9%
Peripheral edema	2.1%	1.1%	2.1%	1.0%	3.5%
Injury-accidental	2.9%	2.3%	3.0%	2.6%	3.2%
Central and peripheral nervous system					
Dizziness	2.0%	1.7%	2.6%	1.3%	2.3%
Headache	15.8%	20.2%	14.5%	15.5%	15.4%
Psychiatric					
Insomnia	2.3%	2.3%	2.9%	1.3%	1.4%
Respiratory					
Pharyngitis	2.3%	1.1%	1.7%	1.6%	2.6%
Rhinitis	2.0%	1.3%	2.4%	2.3%	0.6%
Sinusitis	5.0%	4.3%	4.0%	5.4%	5.8%
Upper respiratory tract infection	8.1%	6.7%	9.9%	9.8%	9.9%
Skin					
Rash	2.2%	2.1%	2.1%	1.3%	1.2%

In placebo- or active-controlled clinical trials, the discontinuation rate due to adverse events was 7.1% for patients receiving CELEBREX and 6.1% for patients receiving placebo. Among the most common reasons for discontinuation due to adverse events in the CELEBREX treatment groups were dyspepsia and abdominal pain (cited as reasons for discontinuation in 0.8% and 0.7% of CELEBREX patients, respectively). Among patients receiving placebo, 0.6% discontinued due to dyspepsia and 0.6% withdrew due to abdominal pain.

The adverse event profile reported for the 83 patients enrolled in the FAP controlled clinical trial was similar to that reported in the arthritis controlled trials. Intestinal anastomotic ulceration was the only new adverse event reported in the FAP trial, regardless of causality, and was observed in 3 of 58 patients who had prior intestinal surgery.

Scheduled upper GI endoscopic evaluations were performed in over 4,500 arthritis patients who were enrolled in five controlled randomized 12-24 week trials using active comparators, two of which also included placebo controls.

Twelve-week endoscopic ulcer data are available on approximately 1,400 patients and 24 week endoscopic ulcer data are available on 184 patients on CELEBREX at doses ranging from 50-400 mg BID. In all three studies that included naproxen 500 mg BID, and in the study that included ibuprofen 800 mg TID, CELEBREX was associated with a statistically significantly lower incidence of endoscopic ulcers over the study period. There was no consistent relationship between the incidence of gastroduodenal ulcers and the dose of CELEBREX over the range studied.

Table 16
Incidence of Gastroduodenal Ulcers from Endoscopic Studies in OA and RA Patients

	3 Month Studies	
	Study 1 (n = 1108)	Study 2 (n= 1049)
Placebo	2.3% (5/217)	2.0% (4/200)
Celebrex 50 mg BID	3.4% (8/233)	---
Celebrex 100 mg BID	3.1% (7/227)	4.0% (9/223)
Celebrex 200 mg BID	5.9% (13/221)	2.7% (6/219)
Celebrex 400 mg BID	---	4.1% (8/197)
Naproxen 500 mg BID	16.2% (34/210)*	17.6% (37/210)*

* $p \leq 0.05$ vs all other treatments

Serious clinically significant upper GI bleeding has been observed in patients receiving CELEBREX in controlled and open-labeled trials, albeit infrequently. Among 5,285 patients who received CELEBREX in controlled clinical trials of 1 to 6 months duration (most were 3 month studies) at a daily dose of 200 mg or more, 2 (0.04%) experienced significant upper GI bleeding, at 14 and 22 days after initiation of dosing. Approximately 40% of these 5,285 patients were in studies that required them to be free of ulcers by endoscopy at study entry. Thus it is unclear if this study population is representative of the general population. Prospective, long-term studies to compare the incidence of serious, clinically significant upper GI adverse events in patients taking CELEBREX vs. comparator NSAID products or placebo have not been performed.

In clinical trials, CELEBREX at single doses up to 800 mg and multiple doses of 600 mg BID for up to 7 days duration (higher than recommended therapeutic doses) had no effect on platelet aggregation and bleeding time.

During the controlled clinical trials, there was an increased incidence of hyperchloremia in patients receiving CELEBREX compared with patients on placebo. Other laboratory abnormalities that occurred more frequently in the patients receiving CELEBREX included hypophosphatemia, and elevated BUN. These laboratory abnormalities were also seen in patients who received comparator NSAIDs in these studies. The clinical significance of these abnormalities has not been established.

Reviewer's comments: There is no safety data beyond six months on the dose of 400 mg BID.

6.1.6. Exploratory subgroup analysis

1. FDA analysis of the number of patients who had >=25% reduction or increase in colorectal polyps in marked areas (either tattoo or using other anatomic markers as specified in the protocol): all patients with assessable colon and/or rectal remnants are included in this analysis (N=78). Five patients who had total colectomy are excluded from this analysis.

Table 17: Number of patients who had reductions or increases in colorectal polyps in marked areas

	Placebo (N=15)	100 mg (N=33)	400 mg (N=30)
Decrease in colorectal polyps			
>=50% decrease	0	4	5
25%-49% decrease	1	7	11
<25% decrease	6	8	7
Increase in colorectal polyps			
>=50% increase	0	1	0
25-49% increase	0	2	0
<25% increase	3	3	2

Among the 28 patients who had >=25% reduction in colorectal polyps, 8 patients had an intact colon (2 on 100 mg BID and 6 on 400 mg BID). Only 3 out of these 8 patients had both assessable rectal and colonic polyps. The other 5 patients did not have assessable rectal polyps. These three patients were on the 400 mg bid dose and had a different magnitude of reduction in

rectal and colonic polyps, e.g., patient 50350039 had a 16% reduction in rectal polyps and a 71% reduction in colonic polyps, patient 50520070 had a 0% reduction in rectal polyps but a 60% reduction in colonic polyps, and patient 50619002 had a 67% reduction in rectal polyps and a 50% reduction in colonic polyps.

Among 9 patients who had a >=50% reduction in the number of colorectal polyps in the marked areas, the mean number of baseline rectal polyps in the marked area is 5 (range: 0 to 12) and the mean number of baseline colonic polyp in the marked areas is 3 (range: 0 to 10).

Among the 19 patients who had 25% to 49% reduction in the number of colorectal polyps in the marked areas, the mean number of baseline rectal polyps in the marked area is 11 (range: 0 to 41) and the mean number of baseline colonic polyps in the marked areas is 2 (range: 0 to 9)

2. FDA analysis of the number of patients who had *subtotal colectomy* and reductions in rectal polyps:

Table 18: Number of subtotal colectomy patients who had reductions in rectal polyps (N=51) by 2 different methods of assessment

	Placebo (N=10)	100 mg (N=23)	400 mg (N=18)
Decrease in rectal polyps in one tattoo area (quantitative)			
>=50% decrease	0	3	3
25%-49% decrease	1	6	7
<25% decrease	4	6	4
Decrease in rectal polyps counts in 2 high-density and 2 low-density areas* by photo review (quantitative)			
>=50% decrease	0	2	1
25%-49% decrease	2	4	6
<25% decrease	1	2	2

*These high density and low density areas were not marked during colonoscopy, therefore the baseline high/low density areas may not be the same high/low density areas at follow-up exam.

18 out of 20 patients who had >=25% reduction in rectal polyps in one tattoo area also had polyp counts in 2 high/2 low density areas. 5 out of

these 18 patients (1 on placebo, 2 on 100 mg BID, and 2 on 400 mg BID) had an increase in polyp counts in 2 high/2 low-density areas. The magnitude of increase ranged from 14% to 300 %. For example, 2 patients on 400 mg BID with a 37% and 70% reduction in rectal polyps in the tattoo area respectively, had a 50% and 89% increase in polyp counts at 2 high/2 low density areas. Likewise, 2 patients on 100 mg BID with a 33% and 40% reduction in rectal polyps in the tattoo area respectively, had a 300% and 80% increase in polyp counts in 2 high/2 low density areas.

3. FDA analysis of the number of patients who had an *intact colon* and reductions in rectal and colonic polyps in tattoo and marked areas (ileocecal valve and appendiceal orifice): N=23

Table 19: Number of patients with an intact colon who had reductions in colorectal polyps in tattoo and marked areas (ileocecal valve and appendiceal orifice)

	Placebo (N=5)	100 mg (N=7)	400 mg (N=11)
Decrease in colorectal polyps:			
>=50% decrease	0	1	2
25%-49% decrease	0	1	4
<25% decrease	2	2	3

The two patients on 100 mg BID who had >=25% decrease in colorectal polyps had NO rectal polyps in the tattoo area at baseline. Out of the six patients on 400 mg bid who had >=25% decrease in colorectal polyps, 3 patients had NO rectal polyps in the tattoo areas at baseline, 1 patient had NO change in the rectal polyps in the tattoo area at follow-up exam and 2 patients had 17% and 67% reduction in the rectal polyps in tattoo areas, respectively, at follow-up exam.

4. FDA analysis of Rectal video tapes using the applicant's data set
Five committee members reviewed 74 rectal videos. Overall condition of the rectum was rated as better, same, worse, or unreadable. Three members agreed on the rating in 72 out of 74 videos and four members agreed on the rating in 52 out of 74 videos.

Table 20: Number of patients with different rating by 3-member or 4-member consensus

Number of Patients w/	Consensus by 3 reviewers			Consensus by 4 reviewers		
	Placebo N=15	100 mg N=30	400 mg N=29	Placebo N=15	100 mg N=30	400 mg N=29
Better	0	5	8	0	2	6
Same	11	19	19	10	16	13
Worse	3	5	1	1	3	1
Unreadable	0	1	0	0	0	0
No consensus	1	0	1	4	9	9

There are 67 patients who had rectal polyp count in one tattoo area and rectal video assessments. 22 patients had >=25% reduction in the rectal polyp count, 38 patients had percent change in rectal polyp count ranging from – 24.9 % to +24.9% and 7 patients had >=25% increase in rectal polyp counts. Among 22 patients who had >=25% reduction in rectal polyps in one tattoo area, only 6 patients were rated "better" by 4-member consensus. On the contrary, for patients who had <=25% decrease in polyp counts or increase in polyp counts, only 2 patients were rated "better" by 4-member consensus.

Table 21: Correlation between percent change in rectal polyp counts and 4-member consensus rating

4-member consensus	↓ polyp count >=25 % N=22	⟷ Polyp count (-24% to +24%) N=38	↑ polyp count >=25% N=7
Better	27.2 % (6)	5.3 % (2)	0 %
Same	22.7 % (5)	63.2 % (24)	42.9 % (3)
Worse	13.6 % (3)	5.3 % (2)	0 %
No consensus	36.4 % (8)	26.3 % (10)	57.1 % (4)

5. FDA analysis of colon video tapes using the applicant's data set
Five committee members reviewed 23 colon video tapes (6 on placebo, 7 on 100 mg and 10 on 400 mg group). 2 patients on 100 mg group and 2 patients on 400 mg were rated "better" by 4 out of 5 Committee members. No patients on placebo were rated "better" by 4-member consensus.

Table 22: Number of patients with different ratings by 4-member consensus

Number of patients w/	Placebo N=6	100 mg BID N=7	400 mg BID N=10
Better	0	2	2
Same	4	3	2
Worse	1	1	2
No consensus	1	1	4

6. FDA analysis of duodenum video tapes using the applicant's data set
Five committee members reviewed 78 duodenum video tapes (17 on placebo, 31 on 100 mg and 30 on 400 mg group). 6 patients on 400 mg group and 1 patients on placebo were rated "better" by 4 out of 5 Committee members.

Table 23: Number of patients with different ratings by 4-member consensus

Number of patients w/	Placebo N=17	100 mg BID N=31	400 mg BID N=30
Better	1	0	6
Same	10	23	18
Worse	1	1	0
No consensus	5	7	6

7. Correlation between the primary and secondary efficacy endpoints. Correlation between the primary efficacy endpoints and secondary efficacy endpoints are assessed by scatter plot and linear regression analysis. There is no correlation between the primary and secondary efficacy endpoints.

7. Summary

7.1. Applicant's summary of pivotal trial results and conclusion

From this study, it was concluded that:

1. CELEBREX, at an oral dose of 400 mg BID, is safe and effective for the regression and prevention of adenomatous colorectal polyps in patients with Familial Adenomatous Polyposis (FAP). This conclusion is supported by the following findings in comparison to placebo:
    - a significant reduction in the number of colorectal polyps
    - a significant reduction in colorectal polyp burden
    - a reduction in mean residual colorectal polyp size
    - a significantly increased percentage of responders (≥25% reduction in colorectal polyps)
    - a reduction in number and percentage of patients in whom disease progressed
    - confirmation of significant clinical benefit in the colon and rectum based on physicians' blinded review of endoscopy videotapes

2. CELEBREX shows a consistent effect across different anatomical regions of the GI tract. This conclusion is supported by the following findings:
    - a reduction in the number of colon polyps
    - a reduction in the number of rectal polyps
    - a reduction in the surface area of the duodenum covered with plaque-like polyps
    - confirmation of significant clinical benefit in the colon, rectum and duodenum based on physicians' blinded review of endoscopy videotapes

3. CELEBREX is well tolerated at oral doses of 100 mg BID and 400 mg BID in patients with FAP.

CELEBREX, at an oral dose of 400 mg BID, provides safe and effective drug therapy for the regression and prevention of adenomatous colorectal polyps which lead to the development of colorectal cancer in patients with FAP. In conjunction with endoscopy surveillance, treatment with CELEBREX may be used as a medical strategy to possibly reduce the number of polypectomies and possibly delay or reduce the extent of colon surgery, thus preserving colonic function.

7.2. FDA summary and comments on the pivotal trial

This pivotal trial enrolled a heterogeneous FAP patient population. 25 out of 83 patients had an intact colon and 13 out of 83 patients had the attenuated FAP phenotype. Results of biomarker studies, family history/pedigree and dietary assessments were not submitted in this sNDA.

Among the three treatment groups (placebo, 100 mg BID, and 400 mg BID), patients on the 400 mg BID were younger and had a shorter interval from colectomy. These imbalances in patient characteristics did not appear to impact on the efficacy results by covariate analysis.
FDA analysis confirmed the applicant's on the primary efficacy endpoint, i.e., the mean percent decrease in colorectal polyp counts (relative to baseline) is greater in patients on 400 mg BID when compared to patients on placebo ($p=0.003$). However, the primary efficacy endpoint of colorectal polyp count was derived from one tattoo area in the rectum and a combination of tattoo area(s) as well as anatomically marked areas in the colon. It is unclear whether changes in polyp counts in these marked areas are reliable surrogates for the changes in polyp burden in the entire colon and/or rectum. Some of the polyps were removed at the 6-month follow-up exam. The number of these polyps requiring removal and their pathology were not submitted in this sNDA.

During the treatment duration of 6 months, CELEBREX appeared to be well tolerated. There were few dropouts and ≥grade 3 toxicities. The two reported deaths were suicide which may not be related to CELEBREX. The applicant's summary of safety data in the arthritis population described incidence of adverse events during treatment ranging from 3 months to 6 months. Most of these patients took CELEBREX at a dose lower than 400 mg BID which is the recommended dose for FAP patients. Therefore, although CELEBREX appeared to be well tolerated at 400 mg BID for 6 months, there is no safety data from arthritis population on this dosage beyond 6 months.

In summary, CELEBREX appears to be well tolerated for a treatment duration of 6 months. There is a statistically significant reduction in mean

percent of colorectal count when comparing patients on 400 mg BID to patients on placebo. However, given that the colorectal polyp count is derived from tattoo and/or anatomically marked areas only, it is unclear whether this reduction in polyp count represents a reduction in the polyp burden in the entire colon and/or rectum. It is known that the entire gastrointestinal mucosa in FAP patients is at risk for developing polyps and/or undergoing malignant changes. Since an extensive panel of biomarker studies was prospectively specified in the protocol, it would be of great interest to examine the results of these studies when available.

Marketing approval based on the results of study 001 assumes that the demonstration of a roughly 30% reduction in colorectal polyps (a surrogate endpoint) in focal area(s) is reasonably likely to predict clinical benefit in FAP patients. Under these circumstances, the accelerated approval regulation could be invoked (Subpart H) and one or more post-approval clinical studies would be required to demonstrate clinical benefit.

If marketing approval (accelerated approval) is recommended, product labeling should address the following unanswered questions regarding the use of CELEBREX in FAP:

- Does use of CELEBREX reduce the incidence of colorectal cancer in FAP patients?
- Can endoscopic surveillance be less frequent on CELEBREX?
- What is the optimal duration of treatment?
- What is the optimal timing of treatment?
  - In teenagers, so that initial colectomy can be delayed?
  - Immediately post-colectomy, so that retention of the rectal stump can be maximized?

It is anticipated that phase IV studies would address some of the unanswered questions raised above.

9 ODAC Meeting

The 64th meeting of the Oncologic Drugs Advisory Committee was held at the Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland. The meeting was chaired by Richard Schilsky, M.D. on December 13 and by Derek Raghavan, M.D. on December 14. The supplemantal NDA of CELEBREX was presented to ODAC on December 14, 1999.

Below are the questions for the ODAC used at the 12/14/99 meeting. The vote counts and commentaries were added by the Committee's Executive Secretary Karen Somers.

Questions to the Committee

I. Persuasiveness of the finding

1. The study endpoint reflects changes in colorectal polyps in focal areas. Overall assessment of videotaped colorectal endoscopies showed improvement in some patients. Treatment was not associated with a statistically significant reduction in duodenal plaque-like polyps compared to placebo. (This question was split into two parts.)

   a. Do you believe the observed focal effect on colorectal polyps is a reasonable indicator of the effect in the whole colon and rectum? (If no, proceed to question II.6).

   YES – 15 NO – 0 Abstain – 0

   b. Do you believe the observed focal effect on colorectal polyps is a reasonable indicator of the effect in the whole gastrointestinal tract? (If no, proceed to question II.6).

   YES – 0 NO – 14 Abstain – 1

2. The study lasted 6 months. Do you believe it provides adequate evidence of a persistent effect on colorectal polyps? (If no, proceed to question II.6).

   YES – 6 NO – 6 Abstain – 3

   The Committee interpreted this question to be asking if the effect would continue if treatment with Celebrex were continued past 6 months.

3. There is only a single study supporting effectiveness. Is the single result so persuasive that you believe it should be accepted as evidence of a sustained reduction in focal polyps? (If no, proceed to question II.6).

   YES – 14 NO – 0 Abstain – 1

II. Meaningfulness of the finding

1. Do you believe that a reduction in colorectal polyp count in FAP patients in focal areas of some magnitude is "reasonably likely" to predict benefit, assuming that all other aspects of patient care are unaltered? Explain

what clinical benefit(s) might be predicted. (If no, proceed to question II.6).

YES – 13 NO – 0 Abstain – 2

2. Do you believe that the observed reduction (about 25% at 6 months) is likely to predict benefit in FAP patients, assuming treatment is otherwise unaltered? Explain. (If no, proceed to question II.6).

YES – 12 NO – 0 Abstain – 3

3. If the answers so far are yes, do you believe, without further data, that we can be reasonably sure (or can draft labeling or other mechanisms to allow assurance) that treatment will not be altered because of a belief that it is now "safe" to delay surgery? Suggestions on how to accomplish this are welcome. (If no, proceed to question II.6).

YES – 11 NO – 0 Abstain – 4

4. Do you recommend approval of Celebrex under the accelerated approval rule for some treatment of FAP? (If no, proceed to question II.6).

YES – 14 NO – 0 Abstain – 1

5. If yes, please consider the indication that should be approved, e.g., for use as an adjunct to usual care (not as a substitute for any aspect of monitoring or surgery that would ordinarily be used) in the treatment of FAP. We would add details of what has, and what has not, been shown. Also consider needed warnings and precautions that should be included in product labeling. (Proceed to III. 1-4)

   The Committee had several suggestions for the labeling, including specific information for patients of established phenotypic FAP, and strong warnings and precautions (perhaps even a Black Box) emphasizing the need for unaltered diagnostic procedures, monitoring and surgical approaches. There are also concerns about drug interactions in these patients with long term use of Celebrex. The sponsor is also urged to study the drug more thoroughly in adolescents.

6. If responses regarding the persuasiveness or meaningfulness of the finding are no, or accelerated approval is not recommended, what would be an appropriate study in FAP patients?

No vote was taken.

III. Post-Approval Study

If accelerated approval is recommended, the applicant is required to study the drug further to verify and describe its clinical benefit.

1. Please comment on the acceptability of the applicant's proposed post-approval study, including the study population (adolescents with FAP), choice of control, and primary efficacy endpoint (the proportion of patients who require colorectal surgery by age 21).

   No vote was taken. Several possible studies were discussed, including an open study, a study of pediatric patients who have not yet expressed the disease phenotype, and a study randomizing patients to different surgeries in the presence of the drug.

2. Note this study tests the possibility that surgery might be delayed without risk to patients. Is the proposed study able to assess that risk?

   There is wide variation among surgeons on the timing of surgery, particularly in adolescents. There is evidence that the development of desmoid tumors is stimulated by surgery and there are also developmental reasons to delay surgery. However, the Committee indicated that, until further studies have been completed, the criteria for surgery should not be changed due to the availability of Celebrex.

3. Do you agree that the proposed study is adequately designed to demonstrate clinical benefit of Celebrex therapy in FAP patients?

   No vote was taken.

4. If the proposed study is not adequate, please comment on what might constitute an adequate study.

10 FDA conclusions

The randomized, double-blind, placebo controlled trial 001 showed that there was a mean 28% decrease in colorectal polyps in focal area(s) in the 400 mg group when compared to the placebo group (p=0.003). The primary efficacy endpoint of percent change in colorectal polyps was derived by one investigator using still photographs. No independent confirmation of these polyp counts was provided by the applicant. FDA counted colorectal polyps in 28 out of 41 patients at St. Mark's. The primary efficacy endpoint in the 400 mg group (N=13) from FDA was very similar to the result from the applicant's. FDA could not verify the polyp counts in the MD Anderson

patients using the submitted photographs. For details, please see section 6.1.3. However, the applicant provided the percent change in colorectal polyps in 71 patients by video counting. Although this method of counting was not prespecified in the protocol, it is an alternative method of counting polyps in the same focal area(s) identified by tattoo and anatomical markers. Furthermore, the video counting was performed under blinded condition. The results showed that there was a mean 29% reduction in the colorectal polyps in focal area(s) in the 400 mg group when compared to the placebo group (p=0.033). The mean percent change in polyps in 400 mg group by video counting (29%) was very similar to the one by still photograph counting (28%). Correlation analysis showed that there was a fair correlation between the percent change in colorectal polyps measured by these two methods. Covariate analysis showed that imbalances in patient age, years since colectomy, colon status, and attenuated FAP status did not have a statistically significant impact on the primary efficacy results derived by either method. The effect on the number of colorectal polyps in the 400 mg group was further supported by the exploratory analysis that more patients in the 400 mg group had >=25% decrease in polyp count and an improvement in the global appearance of colorectum and duodenum.

We feel that it is difficult to asses the effect on polyposis *quantitatively* based on polyp numbers in focal area(s) and the technical challenges associated with the method. However, we agree with the ODAC that CELEBREX at 400 mg appeared to have a statistically significant effect on decreasing polyposis in colorectum when compared to placebo. Whether this partial reduction in polyposis will "likely" result in clinical benefit is a judgement call and will need to be studied further in post-marketing studies.

CELEBREX at 400 mg BID was well tolerated for a treatment duration of 6 months. Safety data on this dose up to one year will be available soon according to the applicant.

11 Recommendation:

This sNDA for CELEBREX is approvable as per the accelerated approval regulation (Subpart H) provided that the applicant will commit to perform phase IV studies to demonstrate the clinical benefit associated with a reduction in polyposis in FAP patients.

/S/ 12-22-99

Judy H. Chiao, MD
Medical Reviewer

/S/ 12/22/99

Julie Beitz, MD
Medical Team Leader

/S/ 12/22/99

John Lawrence, PhD
Statistical Reviewer

/S/ 12/22/99

Gang Chen, PhD
Statistical Team Leader

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