Oncologic Drugs Advisory Committee
Briefing Document

March 12-13, 2003

Celecoxib (Celebrex®) Therapy of Familial Adenomatous Polyposis

New Drug Application (NDA) 21, 156

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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Peapack, NJ

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1. Summary

Familial adenomatous polyposis (FAP) is a rare genetic disease (incidence <1:10,000), characterized by the development of hundreds to thousands of pre-cancerous polyps in the colon, rectum and duodenum. Left untreated, these patients have a 100% lifetime risk of developing colorectal cancer. Surgery is the primary treatment modality in the management of FAP. Prior to approval of celecoxib in FAP, there were no FDA-approved pharmacologic treatments available.

In December 1999, celecoxib was granted accelerated approval to reduce the number of adenomatous colorectal polyps in FAP as an adjunct to usual care. Clinical evidence forming the basis for approval was derived from a randomized, double-blind, placebo-controlled study (FAP-001) that demonstrated that celecoxib is effective in reducing the number of colorectal polyps in patients with FAP. As a condition for approval under Subpart H, Pharmacia reached an agreement with the Food and DrugnAdministration (FDA) to conduct 2 programs to provide additional evidence of clinical benefit. The first, a phenotype suppression program in adolescent patients with genotypic evidence of FAP, is designed to assess the safety and efficacy of celecoxib by documenting a delay in the time to expression of the colorectal adenoma phenotype. The second, an observational FAP registry, is designed to collect data regarding the long-term use and safety of celecoxib in actual clinical practice and to assess the impact of its use on endoscopic surveillance and FAP-related outcomes.

Pharmacia is fully dedicated to completing its post-approval commitments, as exemplified by its completion of subpart H requirements for irinotecan (CAMPTOSAR®) and dexrazoxane (ZINECARD®). The sponsor is similarly dedicated to ensuring completion of the commitments for celecoxib in FAP. Because of the rarity of the disease, special considerations related to conduct of studies in children, and procedural and study design complexities, these programs have proven difficult to plan and initiate. Despite these challenges, the phenotype suppression program has begun in collaboration with the National Cancer Institute (NCI) and 8 academic institutions with expertise in the management of the disease. Extensive work in developing a multi-institutional registry has been undertaken. However, concerns raised by collaborators have dictated a number of reassessments of the study design. Having pursued several alternatives, Pharmacia continues to work toward initiating the registry by 3Q2003.

2. Background

2.1. Familial Adenomatous Polyposis

FAP is a rare genetic disease resulting from an autosomal dominant genetic alteration in the adenomatous polyposis coli (APC) gene (Kinzler 1996). With an annual incidence of <1:10,000, it is estimated that there are approximately 322 new patients for every 3,612,000 births in the United States. Patients with this disease characteristically develop hundreds to thousands of potentially pre-cancerous polyps (adenomas) in the duodenum, colon and rectum beginning in adolescence. Left untreated, these patients have a 100% lifetime risk of developing colorectal cancer. Individuals with FAP are also at risk for developing duodenal cancer, desmoid tumors, and other neoplasias (Spigelman, 1994, Jagelman 1988). To prevent colon cancer development, it is currently recommended that patients with FAP undergo colectomy with ileo-rectal or ileo-anal anastomosis at a time when polyp burden, size, or degree of dysplasia are not amenable to safe endoscopic management. Repeated surgeries (including removal of the remaining rectum or ileal pouch and creation of an ileostomy, or duodenal resection) may be necessary if endoscopic control of polyps in the remaining gastrointestinal tract cannot be achieved.

Given the serious consequences of FAP in terms of cancer risk and need for repeated major surgical interventions, there has been interest in developing a systemic treatment with low toxicity that could reduce polyp burden as an adjunct to surgery.

2.2. Cyclo-oxgenase (COX) Inhibition and Gastrointestinal Neoplasia

One potential pharmacologic target in impeding growth of adenomatous tissue has been the cyclo-oxygenase (COX) enzyme. There are at least 2 COX enzymes present in humans, COX-1 and COX-2 (Fu, 1990). COX-1 is a housekeeping enzyme that mediates the production of prostaglandins responsible for protecting and regulating normal cell function in the gastrointestinal tract and platelets. Under normal conditions, COX-1 is present in most cells and tissues including colon, kidney, spleen, stomach, liver, lung, heart and brain. This differs significantly from the role of COX-2, an enzyme that is rapidly induced at the site of inflammation. Elevated levels of COX-2 are found in many pre-malignant lesions; in particular, it has been demonstrated that COX-2 expression is low to undetectable in normal colorectal mucosa, whereas in the majority of colorectal adenomas and adenocarcinomas, COX-2 expression is increased (Eberhart 1994).

Several lines of evidence have suggested that application of COX-2 inhibitors might have therapeutic utility in reducing colorectal neoplasia. Epidemiological studies have documented that chronic use of nonselective COX-1 and COX-2 inhibitors such as nonsteroidal anti-inflammatory drugs (NSAIDs) can reduce the development of sporadic adenomatous polyps (SAP) and colorectal cancers in humans. *Apc*^{716} mice, models for human FAP due to a truncation mutation in the APC gene, have been shown to develop markedly fewer polyps when a COX-2 knockout mutation is introduced (Oshima, 1996). Similarly, administering a selective COX-2 inhibitor to the rodents suppresses polyp formation in a dose-dependent fashion.

The recent development of selective COX-2 inhibitors, such as celecoxib (Celebrex®), has provided the opportunity to more safely test the hypothesis that selective inhibition of COX-2 might be useful in the prevention or treatment of adenomatous polyps. Clinical

studies of celecoxib in more than 4000 patients with osteoarthritis and rheumatoid arthritis have demonstrated the safety and efficacy of chronic use of celecoxib at doses of up to 400 mg BID, and have documented an improved safety profile relative to NSAIDs (Silverstein 2000).

2.3. Pharmacia Development of Celecoxib for Adenomatous Polyps

Based on these collective data, Pharmacia, working in collaboration with investigators and the NCI, has undertaken a formal clinical program to systematically evaluate the clinical effects of celecoxib in patients with adenomatous polyps. Two principle areas of research have been pursued: use of celecoxib as therapy of adenomatous polyps in patients with FAP and use of celecoxib as prevention of recurrent polyps in patients with SAP. This document will focus on the developmental program in FAP. The intent is to provide information on the study that formed the basis of accelerated FDA approval of celecoxib for FAP and on the ensuing activities that Pharmacia has pursued in meeting regulatory obligations to obtain full approval of celecoxib for FAP.

3. Randomized Study of Celecoxib as Therapy of FAP

3.1. Study Design

Clinical evidence supporting the Food and Drug Administration (FDA) approval of celecoxib (Celebrex®) in the therapy of FAP was derived from a randomized, double-blind, placebo-controlled study conducted to evaluate the effect of the drug in reducing the number and size of colorectal polyps in patients with FAP (Study FAP-001). This study was conducted at 2 centers (University of Texas MD Anderson Cancer Center [MDACC], Houston and St. Marks Hospital, London) experienced in the management of this disease.

Patients with genetically documented FAP who had phenotypically expressed gastrointestinal tract disease were eligible. Following baseline upper and lower gastrointestinal endoscopies, patients were randomized by center with allocation in a ratio of 1:2:2 (placebo, celecoxib 100 mg BID, celecoxib 400 mg BID, respectively). Duration of treatment was 6 months (up to 200 days). Safety and tolerability information was obtained at patient visits and structured interviews at Weeks 2 and 4, followed by monthly contacts until at least 1 month after completing treatment or until resolution of any potential adverse events. At the end of the study, both upper and lower gastrointestinal endoscopies were repeated. The primary efficacy outcome for the study was the percent change from baseline in colorectal polyp number as determined after 6 months of treatment or at treatment withdrawal.

3.2. Study Results

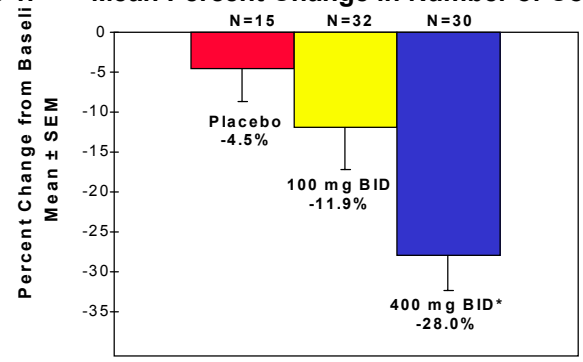
3.2.1. Patient Characteristics

Over a 2-year period, 83 patients were recruited and referred from a wide geographic distribution within both the United States and United Kingdom. Patients ranged in age from 19 to 64 years. All had lower gastrointestinal tract disease with 5 or more polyps $\geq$ 2 mm in size in colon or rectal segments. There was a good balance of important patient characteristics across the study arms.

3.2.2. Efficacy

In the evaluation of the primary endpoint, celecoxib was observed to induce a dose-dependent effect on reduction of polyp number. As shown in Figure 1, celecoxib 400 mg BID for 6 months reduced the number of colorectal polyps by 28.0% from baseline; this change was highly statistically significant compared to the change in polyp number in patients receiving placebo (p=0.003).

Figure 1. Mean Percent Change in Number of Colorectal Polyps



*p=0.003 versus placebo

Evaluation of secondary endpoints supported the primary analysis. Relative to the placebo control group, additional findings in the group receiving celecoxib 400 mg BID included:

- A 30.8% reduction in the number of colon polyps, a 24.3% reduction in the number of rectal polyps, and a 14.5% reduction in area of discrete and plaque-like adenomas in the duodenum.
- A reduction in the percentage of patients who experienced an increase in the number of colorectal polyps (7% with celecoxib 400 BID vs. 20% with placebo).
- A significant increase (p=0.003) in the percentage of patients with a polyp response (>25% reduction in the number of colorectal polyps).
- A 30.7% reduction in colorectal polyp burden (composite measure of polyp size and number)(p=0.001).
- Subjective improvements (p<0.015) in the appearance of the colorectum as determined by 5 experts reviewing videotaped colonoscopies blinded for treatment and timing of endoscopy.
- Subjective improvements (p<0.033) in the appearance of the duodenum as determined by 5 experts reviewing videotaped endoscopies blinded for treatment and timing of endoscopy.

3.2.3. Safety

The adverse event profiles in the groups treated with celecoxib were similar to that in the group treated with placebo.

4. NDA Approval and Post-Approval Commitments

The results of study FAP-001 were submitted to the FDA as NDA # 21-156 on June 24, 1999. On December 14, 1999 the FAP application was the subject of an Oncologic Drugs Advisory Committee (ODAC) meeting at which time the committee voted in favor of accelerated approval. On December 23, 1999 the Food and Drug Administration granted accelerated approval for celecoxib to *"reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP) as an adjunct to usual care (e.g., endoscopic surveillance, surgery.)"* As part of the indication statement, it was also noted that: "*It is not known whether there is a clinical benefit from a reduction in the number of colorectal polyps in FAP patients and it is also not known whether the effects of Celebrex® treatment will persist after it is discontinued. The efficacy and safety of Celebrex® treatment in patients with FAP beyond six months have not been studied*."

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further clinical studies to verify and describe clinical benefit. For the FAP indication, the FDA specifically requested that Pharmacia provide a better understanding of how celecoxib might improve patient prognosis in terms of time to surgery, cancer, or death. In addition, the safety of celecoxib beyond 6 months had not been established in FAP patients. Therefore, 2 Subpart H clinical commitments were specified in the FDA's December 23, 1999 accelerated approval letter – a phenotype suppression program in adolescent patients with genotypic evidence of FAP and an observational FAP registry in patients with phenotypically apparent disease.

In addition, Pharmacia committed to provide further information on the results from the FAP-001 study when they became available and to initiate an SAP development program.

In the December 23, 1999 approval letter issued by the FDA, Pharmacia and FDA agreed to the following Subpart H post-approval commitments:

> *"1. A randomized controlled trial in familial adenomatous polyposis (FAP) that will verify and describe the clinical benefit of Celebrex in this population. Your proposal for a placebo-controlled study of adolescents with FAP aged 12 to 19 years who are genotypically positive but phenotypically negative is acceptable. The study should be completed and submitted to FDA with due diligence.*
>
> *2. A long-term registry of clinical outcomes in FAP patients. Your proposed for enrolling patients aged 12 years or above to Celebrex 400 mg BID is acceptable. Eligible patients would include those who are phenotypically positive who a) have not had primary prophylactic surgery, b) have not had secondary surgery, or c) have had both primary and secondary surgery. Time to FAP-related events (FAP-related surgery, gastrointestinal cancer, desmoids, or death) and adverse events will be collected and compared to untreated historical controls. Information collected on registry patients should be submitted to the NDA on an annual basis."*

5. Activities Pursued by Pharmacia to Meet Subpart H Post-Approval Commitments

The following sections document the activities that have been undertaken by Pharmacia, working in collaboration with investigators, the NCI, and the FDA, to meet the Subpart H post-FAP approval commitments.

5.1. FAP Phenotype Suppression Studies

FAP is a rare condition and genotypically positive, phenotypically negative patients are only a subset of the total FAP population. Because of the limited number of patients available for study, it was necessary to conduct this trial at centers that maintain data on families with FAP. The MDACC had successfully conducted the FAP-001 pivotal trial and had the expertise, motivation, data quality standards, and sufficient patient population to conduct this trial. Based on this experience, the NCI and Pharmacia selected MDACC to design, implement, and coordinate the FAP phenotype suppression trial.

After celecoxib approval for FAP was granted, MDACC began to initiate planning for this trial. In April 2000, the "Intent to Submit a Study Proposal" was submitted to the NCI. In addition to working with NCI, MDACC began coordination with 7 other institutions with expertise in the management of FAP patients.

The original protocol described a phase III, 2-arm, double-blinded, placebo-controlled study. However, concerns were raised by the investigators regarding the conduct of this trial. There was limited information regarding the safety of the approved FAP dose in an adolescent population. To address this concern, a development plan that included both a Phase I and Phase III study was submitted to FDA in January 2001. On April 5, 2001 the FDA reviewed the proposal and agreed to this approach.

Plans for the Phase I trial elicited considerable discussion following a recommendation by the NCI that a placebo group be included in this initial study. Investigators were concerned about the inclusion of a placebo group in a limited Phase I setting (18 patients total). The NCI contended that in the cancer prevention setting, the inclusion of a small placebo cohort would permit a better assessment of adverse events. Because of these discussions, the protocol required 3 revisions over the course of a year before consensus could be reached by Pharmacia, MDACC and NCI (See Appendix 1). A final protocol design was ready for institutional review board (IRB) submission in January 2002.

Because this study was in a pediatric population, it was originally felt that an orally dispersible tablet formulation, which was in development, would be desirable. Before the protocol could be implemented, tablet development issues arose, necessitating a change in formulation from tablets to commercially available capsules and requiring an additional protocol revision. Subsequent to resolution of these issues, the revised protocol was resubmitted to the MDACC IRB in September 2002 and was approved by the NCI in November 2002. The phase I study was initiated in December 2002 and as of January 2003 has enrolled the first cohort of 6 patients. Per protocol, the enrollment of a second cohort of patients should begin in 3 months.

As can be observed from this sequence of events, finalizing a development plan that would be acceptable to investigators, the NCI, the FDA, and Pharmacia has proven to be

complex. Detailed information regarding the timelines for the interactions among the MDACC, the NCI, the FDA, and Pharmacia is provided in Appendix 1.

5.2. FAP Registry Study

At the time of the December 14, 1999 ODAC meeting there was extensive discussion regarding the difficulties in establishing an appropriate post-approval study in FAP and the feasibility of a registry trial was discussed. In the December 23, 1999 accelerated approval letter, as part of the subpart H commitment, the FDA and Pharmacia agreed to the establishment of a FAP patient registry that would follow patients who receive celecoxib and compare outcomes in these patients to untreated historical controls.

Mindful of these commitments, Pharmacia began further development work on the registry protocol. In consultation with experts, it was agreed that a registry could be established, but there was concern that the data might have relatively limited value. Since celecoxib had just been approved for use in FAP, the types of patients who would receive the drug in actual clinical practice had not been characterized; as a consequence, the characteristics needed to define a matched control group could not be identified. It was also noted that changes and improvements in therapeutic approaches or treatment patterns over time might confound comparison with a historical control. Concern was raised that the complexity of the medical, psychological, and social considerations that are integrated into surgical decisions would introduce variability in assessing time to FAP event. It was also pointed out that time to FAP event may be quite long (over 10 years) in many patients, making adequate duration of follow-up impractical.

Because of these concerns, Pharmacia sought to develop an alternative strategy that would provide long-term safety and efficacy data. In January 2001, Pharmacia submitted to the FDA a proposal for a trial that would be an alternative to the registry trial. That trial, to be conducted by the NCI and ILEX, would have provided controlled data on the use of celecoxib versus difluoromethylornithine (DFMO) in FAP patients. However, at the April 5, 2001 meeting with the FDA, this study was rejected as not providing direct data on the clinical benefit of celecoxib and not addressing long-term safety. While the FDA acknowledged the limitations of the registry information, it considered this approach preferable.

In May 2001, Pharmacia again began planning for a registry trial. Because of the successful relationship with MDACC on the FAP-001 trial, MDACC was contacted to begin the process of setting up a registry study. Shortly thereafter, MDACC discussed the concept with the Collaborative Group of the Americas on Inherited Disease (CGA), a consortium of 17 registries and clinics in the US, Canada, and South America. A formal proposal for a prospective registry study was developed, presented, and endorsed at the CGA annual meeting in October 2001. Subsequently, the concept of a web-based registry was developed, a full protocol for a web-based study was written, and the protocol was sent to the CGA for review in April 2002. However, upon further consideration, response to this protocol by the CGA was not positive. It was felt that data entry would be too labor intensive for health care providers thereby limiting collection of data.

Given these concerns, MDACC worked with Pharmacia to revise the protocol, proposing that data be entered on a website directly by patients and that health care provider

involvement be limited to verification of patient-derived data. It was felt that the FAP population was motivated, was very aware of and educated on their condition, and could provide accurate information on their condition and treatment.

The revised web-based patient-entry protocol was presented to various collaborators and genetics counselors who expressed willingness to participate in this protocol and encourage their patients to register. At the same time, the patient questionnaires were prepared and provided to Pharmacia for review. The prototype web-based registry was completed in December 2002 and the protocol was submitted to the MDACC IRB.

The MDACC IRB reviewed the protocol in January 2003. It did not recommend approval of the protocol. The IRB cited lack of source data verification and patient confidentiality as reasons for disapproval.

Pharmacia has continued to work to conduct a registry trial in order to fulfill our Subpart H commitments. To that end, Pharmacia is in active discussions with several large well-established, IRB-approved, FAP registries that have agreed to allow use of their databases and are willing to assist in the development of this study. Given that there are currently several years of experience of celecoxib use in clinical practice, it may now be possible to define the characteristics of FAP patients receiving the drug and to identify a matched historical control population. It is anticipated that a revised registry protocol will be submitted to FDA by 2Q2003. Detailed information regarding the timelines for the interactions among the MDACC, CGA, the FDA, and Pharmacia is provided in Appendix 2.

6. Status of Subpart H Post-Approval Commitments

6.1. FAP Phenotype Suppression Studies

6.1.1. Background

Originally conceived as a single, phase III trial, the program has been modified to also include a phase I study to assess safety and dose-ranging in the adolescent population.

6.1.2. Phase I Study

6.1.2.1. Title

Phase I pilot toxicity/method validation study of celecoxib in phenotype- or genotype-positive children with familial adenomatous polyposis

6.1.2.2. Study Sites

- MDACC
- Texas Children's Hospital
- Cleveland Clinic

6.1.2.3. Primary Objective

To establish a safe dose of celecoxib in adolescents

6.1.2.4. Patient Population

Patients between 10 and 14 years of age (inclusive) with FAP either manifest as genotypic evidence of APC mutation but without clinical evidence of polyposis or as phenotype-positive disease with a non-surgical adenoma burden.

6.1.2.5. Study Design

A dose-escalation design in 3 successive cohorts of 6 patients (18 patients total) is being employed to determine the highest safe dose of celecoxib over the dose range to be evaluated. In each cohort, 4 participants will receive celecoxib and 2 participants will receive placebo. Dose levels of celecoxib include 2 mg/kg BID, 4 mg/kg BID or 8 mg/kg BID (approximating 100 mg BID, 200 mg BID, and 400 mg BID, respectively, for patients = 50 kg). Treatment will proceed for 3 months in each cohort. Unblinding will be carried out following completion of treatment in each cohort. If a dose level is well tolerated, dose escalation will proceed in the subsequent cohort.

6.1.2.6. Status

- First patient in: December 2002.
- Current accrual: 6 patients
- Estimated last patient in: 4Q2003
- Estimated final analysis: 1Q2004

6.1.3. Phase III Study

6.1.3.1. Title

Phase III study of celecoxib in genotype-positive children with familial adenomatous polyposis

6.1.3.2. Study Sites

- MDACC
- Texas Children's Hospital
- Cleveland Clinic
- Memorial Sloan Kettering Cancer Center
- Creighton University
- University of California, San Francisco
- Mt Sinai Hospital, Toronto
- St. Marks Hospital, London
- Roswell Park Cancer Center (possible)
- Northwestern University (possible)

6.1.3.3. Primary Objective

To determine the efficacy of celecoxib versus placebo in delaying the time to expression of the colorectal adenoma phenotype (first adenomatous polyp) in adolescent asymptomatic carriers of APC mutations

6.1.3.4. Patient Population

Patients between 10 and 18 years of age (inclusive) with the APC-mutation but without clinical evidence of polyposis

6.1.3.5. Study Design

A total of approximately 240 patients will be allocated in a 2:1 randomization to receive either celecoxib BID (dose to be determined in the phase I study) or placebo BID. Treatment will be continued for up to 5 years. Compliance, adverse event, and concomitant medication assessments will be monitored using a symptom questionnaire at Baseline, and at Months 1, 2, 3, 4, 5, 6 then annually until study completion. Plasma samples for pharmacokinetic analysis of trough drug levels will be collected at Baseline, Month 6, and Year 1. Assessment of endoscopic and tissue-based biomarker endpoints will be conducted at baseline and annually thereafter for 5 years.

6.1.3.6. Status

- First patient in: 1Q2004
- Estimated last patient in: 3Q2006
- Estimated final analysis: 4Q2011

6.2. FAP Registry Study

6.2.1. Background

As expressed in the original FDA approval letter of December 23, 1999, the study should attempt to assess time to FAP-related events (eg, FAP-related surgery, gastrointestinal cancer, desmoids formation, or death) in celecoxib-treated patients relative to untreated historical controls. At a meeting between the FDA and Pharmacia in April 2001, the FDA further indicated that the registry trial should seek to detect unintended or unforeseen effects of actual celecoxib use in substituting for usual care. The FDA indicated that there was a realization that new therapies and differences in clinical practice might confound analysis. For this reason, a strict statistical analysis of data need not be performed and data would only be employed to identify trends and rough estimates of effect. The FDA suggested that patients currently not on trials and those completing other trials (such as the phenotype suppression study) might be included in the registry.

6.2.2. Proposed Registry Study

6.2.2.1. Title

An observational registry assessing clinical outcomes in patients with familial adenomatous polyposis receiving celecoxib (Celebrex®) and other therapies

6.2.2.2. Study Sites

- MDACC (possible)

- Cleveland Clinic (possible)
- St. Marks Hospital, London (possible)
- Danish Polyposis Registry (possible)

6.2.2.3. Objectives

- To describe characteristics of the population of patients with FAP who receive celecoxib in clinical practice
- To describe current patterns of celecoxib use in the disease management of FAP
- To describe the long-term safety of celecoxib in patients with FAP
- To assess the extent to which use of celecoxib may alter current approaches to the management of FAP, particularly focusing on frequency of endoscopic surveillance and timing of surgery
- To evaluate long-term treatment with celecoxib in relation to other interventions or to no treatment by estimating the incidence of FAP-related events (FAP-related cancers, desmoid tumors requiring procedural intervention, symptoms related to FAP that require hospitalization or procedural intervention, FAP-related surgery, or death related to FAP [i.e., as a consequence of FAP, FAP complications, or a procedure or drug used to treat FAP-related medical problems])

6.2.2.4. Patient Population

Patients who are at least 12 years of age; have a diagnosis of FAP based on the expression of the FAP phenotype and/or molecular diagnosis of pathologic APC-gene mutation have endoscopically assessable colonic, rectal and/or gastroduodenal segment; and have undergone endoscopy within the past year.

6.2.2.5. Study Design

As currently envisioned, the study will be performed as a case-matched control study in patients already participating in existing registries.

- Patients from existing registries will be identified retrospectively (back to January 2000) and prospectively (until 2005). These patients will be followed for up to 5 years (2008). Attempts will be made to collect information regarding disease history, specific indication for celecoxib use, doses of celecoxib used, adverse events, concomitant medications, frequencies of endoscopy, endoscopy findings, and FAP-related events. Assessment of this population of patients will allow description of the types of patients who are receiving celecoxib in clinical practice, patterns of celecoxib use in the disease management of FAP, and a description of long-term celecoxib safety.
- Based on the clinical characteristics (eg, age, gender, baseline polyp burden, extent of prior surgery, timing of initiation of celecoxib in the disease process) of the patients receiving celecoxib, historical controls matched for these characteristics will be identified from among registry patients. The frequency of endoscopies and the time to FAP events will be assessed in these patients and the practicality, timelines, and final statistical considerations in comparing the celecoxib-treated population with this

population will be defined. It is hoped that this approach may allow description of the extent to which use of celecoxib may alter current approaches to the management of FAP or may prolong the time to FAP-related events.

6.2.2.6. Status

- First patient in: 3Q2003
- Estimated last patient in: 3Q2005
- Estimated matching case controls: 1Q2006
- Estimated final analysis: 3Q2008

7. Additional Commitments NDA # 21-156

7.1. Study FAP-001 – Additional Data

Although not a condition of accelerated approval, Pharmacia offered to provide additional information to the FDA regarding the FAP-001 study. The following information was submitted to the FDA in May 2001:

- Data on the number of polypectomies performed and on the histology of polyps removed (including diagnosis of malignancy), with a correlation of polypectomy findings with observed reduction in polyp counts for each treatment arm
- Biomarker data (eg, crypt morphology and apoptotic index, p53 expression, COX messenger RNA/protein expression, etc.) correlated with the observed reduction in polyp counts for each treatment arm
- Data on dietary habits at baseline and on study with an analysis of impact of dietary factors on polyp reduction if imbalances across arms were noted

7.2. SAP Prevention Studies

Two large, phase III, randomized, double-blind, placebo-controlled, multinational trials (submitted under NCI IND 51,926 and Pharmacia IND 61,302) evaluating the efficacy and safety of celecoxib in SAP prevention have completed enrollment of a total of 3594 patients. Follow-up is ongoing and the 3-year efficacy and safety results from both trials will be available by 1Q2005. Two independent data safety monitoring boards meet every 6 months to review these studies, assess safety, and make recommendations regarding the continued conduct of the trials.

8. Conclusions

Inherent challenges in conducting studies in a rare disease have complicated completion of the Subpart H commitments to obtain full approval for celecoxib in FAP. To address these challenges, Pharmacia has partnered with both the NCI and multiple institutions to complete these commitments. The sponsor has successfully initiated the phenotype suppression program and remains committed to initiating an FAP registry.

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10. Appendices

10.1. Appendix 1: FAP Phenotype Suppression Program – Developmental Timeline

Action Date	Action
December 1999	FDA grants accelerated approval for Celecoxib in FAP
April 2000	MDACC filed "Intent to Submit Study Proposal" to NCI, Division of Cancer Prevention
June 2000	MDACC submits proposal to NCI
August 2000	NCI completes review of proposal and sends to MDACC
October 2000	MDACC submitted first draft of protocol to NCI
January 2001	NCI review of protocol received at MDACC
February 2001	Revised protocol submitted to NCI
May 2001	NCI review of protocol received at MDACC
August 2001	MDACC received protocol review from Pharmacia
September 2001	Revised protocol sent to NCI
October 2001	NCI review of protocol received at MDACC
December 2001	Revised protocol sent to NCI
January 2002	NCI approval of protocol with minor revisions
February 2002	Protocol sent to MDACC Office of Research Administration for review
March 2002	MDACC Clinical Research Committee approves protocol
March 2002	MDACC IRB approved protocol
May 2002	MDACC received NCI approval for activation of protocol
June 2002	Site initiation meeting held at MDACC – Pharmacia informs team that there is a problem with stability of oral dispersible formulation
June 2002	MDACC PI meets with Phase II study collaborators at St. Mark's Hospital London
July 2002	Cleveland Clinic Foundation submits protocol to IRB
July 2002	Texas Children's Hospital submits protocol to IRB
July 2002	Executed "Supported Trial Agreement" returned to Pharmacia by MDACC
August 2002	Texas Children's Hospital IRB approves protocol
August 2002	Protocol revised to incorporate use of celecoxib capsules
August 2002	Protocol sent to MDACC IRB
September 2002	MDACC IRB approves protocol
November 2002	NCI approves protocol
December 2002	First patient randomized to protocol

10.2. Appendix 2: FAP Registry Program – Developmental Timeline

Action Date	Action
December 1999	FDA grants accelerated approval for Celecoxib in FAP
February 2000	Discussion with experts
December 2000	Submission of alternative proposal to FDA
April 2001	Pharmacia meets with FDA to propose alternate controlled study celecoxib vs. DFMO. FDA reiterates its desire for a registry trial
May 2001	Pharmacia meets with internal committee to gain funding for trial and pursue cooperative group CGA
May 2001	Pharmacia contacts MDACC and asks if they will write protocol and submit budget
June 2001	MDACC states interest in setting up Registry, with grant from PHA. Further stating that patients to be entered from current registry, from DFMO and Phenotype suppression studies, and from CGA physicians who are interested in participating.
August 2001	MDACC sends copy of a registry proposal written in 6/2000, which is basis for current proposal
August 2001	Pharmacia sends comments regarding protocol endpoints to MDACC
August 2001	Pharmacia provides IT support to MDACC for registry development
September 2001	MDACC rewrites protocol
October 2001	CGA meeting. Protocol concept endorsed by CGA members
November 2001	MDACC sends revised version of protocol to Pharmacia
March 2002	MDACC confirms that CGA will enter patients on registry protocol
April 2002	Site map for Registry sent to PHA. Protocol to be sent to CGA members for review. Budget proposed to PHA by MDACC.
July 2002	Budget approved by PHA. As a result of lack of enthusiasm from the CGA physicians, the registry protocol was modified to include patients entering their own data
October 2002	Registry presented at CGA: Patient questionnaire sent to PHA.
November 2002	Prototype of web site scheduled for Nov 23
December 2002	Current version of Web site prototype sent to PHA. MDACC IRB approval needed.
January 2003	MDACC IRB rejects web-based registry protocol
February 2003	Revised center-based registry protocol under development