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Celecoxib (Celebrex®) Therapy for Familial Adenomatous Polyposis (FAP)

NDA 21-156

"AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION"

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Pfizer, Inc.
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1. SUMMARY

Familial adenomatous polyposis (FAP) is a rare genetic disease (mean annual incidence of 1-2 new cases diagnosed per million inhabitants), characterized by the development of hundreds to thousands of pre-cancerous polyps in the colon, rectum and duodenum. Left untreated, patients with FAP 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.

Pfizer, 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 familial adenomatous polyposis. This document provides information on the study that formed the basis of accelerated FDA approval of celecoxib for FAP and on the ensuing activities that Pharmacia/Pfizer has pursued in meeting regulatory obligations to obtain full approval of celecoxib for FAP.

In December 1999, celecoxib (Celebrex®) was granted accelerated approval for reduction of the number of adenomatous colorectal polyps in patients with 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). As a condition for approval under Subpart H, Pharmacia, now Pfizer, reached an agreement with the Food and Drug Administration (FDA) to conduct 2 programs to provide additional evidence of clinical benefit. The first commitment agreed with FDA was a genotype-positive phenotype negative study in young patients. Changes in the design of this study have already been discussed in detail and agreed with by the FDA. The new program will study phenotype suppression in young patients with genotypic evidence of FAP. It will assess the safety and efficacy of celecoxib by documenting reduction in the rate of treatment failure for subjects treated with celecoxib versus subjects treated with placebo. Treatment failure is defined as the appearance of ≥ 20 polyps at any colonoscopy during the study or a diagnosis of colorectal malignancy. The second commitment, 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. Pfizer has conducted extensive work on both of these commitments.

In order to conduct the Phase III randomized placebo-controlled study in adolescents with FAP, it was first necessary to identify a safe and well-tolerated dose in this population. A Phase I dose finding study in 10-14 year old subjects (age of first screening colonoscopy) was started in December 2002 and the last subject was enrolled in June 2004. The Data Safety Monitoring Board (DSMB) reviewed the safety results from this study on December 16, 2004 and recommended that the Phase III study proceed with the 16mg/kg/d dose. The final design for the confirmatory trial, Protocol A3191193: "A Phase III Placebo-controlled Trial of Celecoxib in Genotype Positive Subjects with Familial Adenomatous Polyposis", was submitted for a Special Protocol Assessment to the Division of Oncology Drug Products on June 21, 2005. Agreements were reached regarding the study population and primary endpoint. The study start-up activities are on track for a projected first subject to be enrolled in January 2006.

Activity on the Celebrex FAP registry is ongoing in five countries. After having evaluated and discussed other alternative options and various study designs with key experts in the management of FAP and with health authorities, Pfizer initiated the registry on September 1, 2004. There are currently 16 patients and 1 matched control contained in the registry.

Pfizer has demonstrated its dedication to completing its post-approval commitments by its completion of the 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 a subset of young patients, and procedural and study design complexities, these programs have proven difficult to plan and initiate but are currently ongoing.

2. BACKGROUND

In 2004, it was estimated that cancers of the breast, prostate, bladder, colon/rectum, lung/bronchus, and oral cavity/pharynx will account for 856,760 new cancer diagnoses and 307,590 deaths in the United States alone (Jemal 2004).

Increasing understanding of the multi-step process leading to the development of cancer, both from a pathological and molecular level, has blurred the distinction between premalignancy and malignancy, and has given the opportunity to intervene earlier in the disease process. Identification of high-risk intraepithelial neoplasia (IEN) lesions and high-risk individuals is critical for development of appropriate therapies including the development of newer molecular therapies. A highest risk IEN lesion such as adenomatous polyps, abundantly found in FAP patients is especially appropriate for development of new therapies.

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 birth incidence of <1:10,000 it is estimated that there were approximately 409 newborns affected with the disease among the total 4,089,950 live births reported in the United States in 2003 (Martin 2005). Published epidemiological data indicate that the mean annual incidence of FAP ranges from 0.9 to 1.9 new cases diagnosed per million inhabitants with prevalence rates ranging from 2.6 to 4.6 cases of affected persons with the disease per 100,000 persons at a given point in time (Bülow 2003). Median age at diagnosis in FAP patients has been reported as 22 years (range 3-65), with similar proportions of men and women. The disease is characterized by the development of hundreds of colorectal pre-cancerous lesions (adenomas) beginning in adolescence, some of which progress to cancer by the fourth decade unless resection has taken place. Before the introduction of screening and prophylactic surgery, the average age at death was 41.8 years (Bussey 1975). Currently, a combination of screening, surveillance and surgical procedures, has substantially reduced the risk of colorectal cancer with resulting improvement in survival.

The standard of care has long been considered to be prophylactic colectomy with either an ileorectal anastomosis (IRA) or ileo pouch-anal anastomosis (IPAA) at diagnosis. IPAA is a major surgical procedure with 2 to 6% mortality. The recognized relative risk of dying in FAP patients after surgery is 3.35 times higher than the risk in the general population (Nugent 1993). Despite this, repeated surgeries may be necessary when full control of polyps in the remaining gastrointestinal tract cannot be achieved. In addition to these risks, FAP patients remain at a higher risk of developing other malignancies (Spigelman, 1994, Jagelman 1988).

Given the serious consequences of FAP in terms of cancer risk and need for repeated major surgical interventions starting early in life, 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-oxygenase (COX) Inhibition and Gastrointestinal Neoplasia

The cyclo-oxygenase (COX) enzyme system has been identified as a potential target for pharmacologic agents that could prevent or impede the growth of adenomatous tissue. 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 use 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. Intestinal polyp formation was markedly reduced in the *Apc delta*⁷¹⁶ mouse model for human FAP when a COX-2 knockout mutation (ptgs2) was introduced (Oshima, 1996). This study also demonstrated that administration of a selective COX-2 inhibitor to these mice resulted in a dose dependent suppression of polyp formation.

Selective COX-2 inhibitors, such as celecoxib, have provided the opportunity to test the hypothesis that selective inhibition of COX-2, without inhibiting COX-1, 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 celecoxib use at doses of up to 400 mg BID, and have documented an improved safety profile relative to standard dosing regimens for non-selective NSAIDs (Silverstein 2000).

2.3. Development of Celecoxib for Adenomatous Polyps

Based on these collective data, Pfizer, 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 familial adenomatous polyposis. 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/Pfizer has pursued in meeting regulatory obligations to obtain full approval of celecoxib for FAP.

2.4. Celecoxib and Cardiovascular Risk

Presently, there is a focus on the cardiovascular safety of NSAIDs and COX-2 selective inhibitors. For celecoxib, cardiovascular safety was evaluated in two randomized, double-blind, placebo-controlled, three-year studies involving patients with Sporadic Adenomatous Polyps treated with celecoxib. The first of these studies was the APC (Prevention of Sporadic Colorectal Adenomas with Celecoxib) study, which compared celecoxib 400 mg twice daily (N=671) and celecoxib 200 mg twice daily (N=685) to placebo (N=679). Safety information from this trial demonstrated a dose-related increase in serious cardiovascular events (mainly myocardial infarction [MI] at celecoxib doses of 200 mg and 400 mg twice daily compared to placebo). The cumulative rates of serious cardiovascular thrombotic events began to differ between the celecoxib treatment groups and placebo after approximately one year of treatment. There were 2.8 to 3.1 years of follow-up in the APC trial except those patients who died earlier. The relative risk (RR) for the composite endpoint of cardiovascular death, MI, or stroke was 3.4 (95% CI 1.4 – 8.5) for the higher dose and 2.5 (95% CI 1.0 – 6.4) for the lower dose of celecoxib compared to placebo. The absolute risk for the composite endpoint was 3.0% for the higher dose of celecoxib, 2.2% for the lower dose of celecoxib, and 0.9% for placebo. The second long-term study, PreSAP (Prevention of Colorectal Sporadic Adenomatous Polyps) compared celecoxib 400 mg once daily to placebo. Safety information from this trial demonstrated no increased cardiovascular risk for the composite endpoint of cardiovascular death, MI or stroke. The reason for the differing results for CV events in the APC and PreSAP trials is not known. Clinical trials of other COX-2 selective and nonselective NSAIDs of up to three-years duration have shown an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. As a result, all NSAIDs are considered potentially associated with this risk (Celebrex 2005, US Package Insert).

Cardiovascular safety outcomes were also evaluated in the CLASS trial. Kaplan-Meier cumulative rates for investigator-reported serious cardiovascular thromboembolic adverse events (including MI, pulmonary embolism, deep venous thrombosis, unstable angina, transient ischemic attacks, and ischemic cerebrovascular accidents) demonstrated no differences between the celecoxib, diclofenac, or ibuprofen treatment groups. The cumulative rates in all patients at nine months for celecoxib, diclofenac, and ibuprofen were 1.2%, 1.4%, and 1.1%, respectively. The cumulative rates in non-ASA users at nine months in each of the three treatment groups were less than 1%. The cumulative rates for myocardial infarction in non-ASA users at nine months in each of the three treatment

groups were less than 0.2%. There was no placebo group in the CLASS trial, which limits the ability to determine whether the three drugs tested had no increased risk of CV events or if they all increased the risk to a similar degree (Celebrex 2005, US Package Insert).

The increased CV risk with celecoxib (Celebrex) observed in APC trial resulted in a re-evaluation of the benefit and risk balance by Pfizer, health authorities, including FDA, and investigators. As a result of guidance from the Arthritis/Drug Safety and Risk Management Advisory Committees and FDA's scientific conclusions, the labeling for celecoxib was revised to incorporate this new risk information. This extensive benefit risk assessment also directly affected the conduct of the Celebrex FAP program.

It is important to understand the risk and benefit of pharmacological intervention in patients with FAP. FAP is a rare genetic disease resulting from an alteration of a tumor suppressor gene and diagnosis usually is made when patients are teenagers. By their late teens, FAP patients have hundreds to thousands of adenomas of the colon and these invariably progress over time. The adenomatous polyp is a recognized cancer precursor and, since polyp number and age positively correlate with an increased risk of cancer, patients with FAP will ultimately develop colorectal cancer (CRC) and die in their forties if left untreated. Surgical prophylaxis has dramatically reduced this cancer risk, even if at a significant cost in morbidity.

Therapeutic intervention is justified by the significant lifetime cancer risk and lack of alternative therapies. CV risk for patients with FAP is expected to be comparable to the age matched general population and will have similar known CV risk factors (hypertension, smoking, cholesterol, etc.). Discussion on the benefit versus risk of celecoxib in FAP needs to consider, in terms of age, frequency of CV risk factors, the potential risk of treatments and lifetime cancer risk. The use of celecoxib in FAP patients is appropriate when considering the possible benefit versus possible risk or the use of alternative pharmacotherapies.

3. RANDOMIZED STUDY OF CELECOXIB AS THERAPY OF FAP (STUDY FAP-001)

3.1. Study Design

Clinical evidence supporting the Food and Drug Administration (FDA) approval of celecoxib (Celebrex) in the treatment 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) with extensive experience in the management of this disease.

Patients with 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.

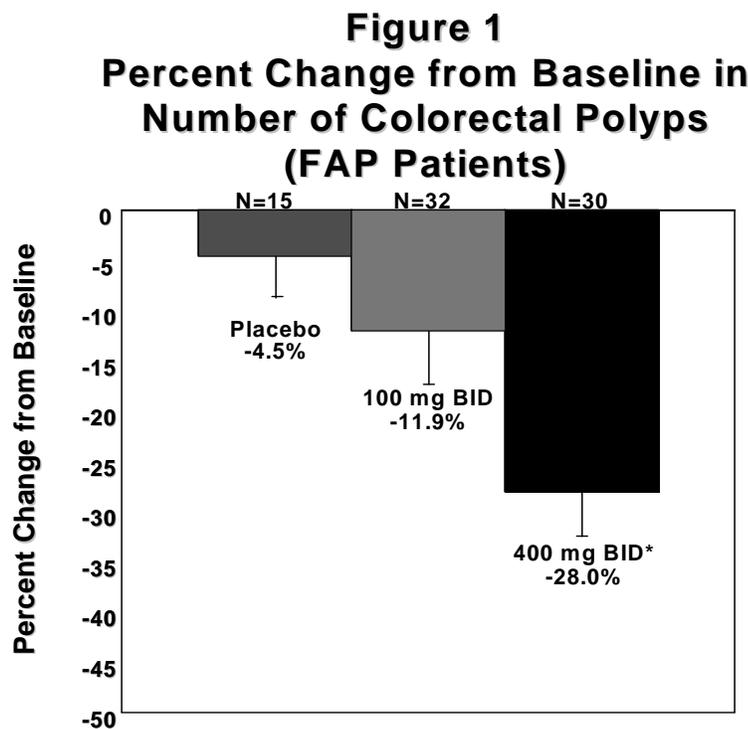
3.2. Study Results

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. Patient characteristics across the study arms at baseline were similar.

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 average of 28.0% from baseline; this mean change was highly statistically significant compared to the mean change in polyp number in patients receiving placebo ($p=0.003$).



* $p=0.003$ versus placebo

The reduction from treatment with 100 mg BID was greater than placebo but did not reach statistical significance. For the 400 mg BID group, 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:

1. A 30.8% reduction in the number of colon polyps, a 24.3% reduction in the number of rectal polyps, and 14.5% reduction in area of discrete and plaque-like adenomas in the duodenum.
2. 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).
3. A significant increase ($p=0.003$) in the percentage of patients with a polyp response ($> 25\%$ reduction in the number of colorectal polyps).
4. A 30.7% reduction in colorectal polyp burden (composite measure of polyp size and number) ($p=0.001$).
5. Subjective improvements in the 400mg BID group ($p<0.015$) in the appearance of the colorectum as determined by 5 experts reviewing videotaped colonoscopies blinded for treatment and timing of endoscopy.
6. Subjective improvements in the 400mg BID group ($p=0.033$) 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 the sponsor to 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 the December 23, 1999 approval letter issued by the FDA, the sponsor 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. The proposal for a placebo-controlled study of adolescents with FAP aged 12 to 19 years who are genotypically positive but phenotypically negative was acceptable. The study should be completed and submitted to FDA with due diligence.*
- 2. A long-term registry of clinical outcomes in FAP patients. The proposed study will enroll patients aged 12 years or above to Celebrex 400 mg BID. 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 AND PFIZER TO MEET SUBPART H POST-APPROVAL COMMITMENTS

The following sections describe the activities that have been undertaken by Pfizer, working in collaboration with investigators, the NCI, and the FDA, to meet the Subpart H post-FAP approval commitments. Appendices 1 and 2 list the chronology of events for the FAP Phenotype Suppression and Registry studies, respectively.

5.1. FAP Phenotype Suppression Studies

The conduct of an FAP phenotype suppression study is complicated by the low incidence of FAP in the general population and with the added challenge of identifying and enrolling a subset of the FAP population who are genotypically positive and phenotypically negative. Because of the limited number of patients available for study due to the rarity of the disorder, it was necessary to conduct this trial at centers that maintain data (patient registries) on families with FAP. The M.D. Anderson Cancer Center (MDACC) had successfully conducted the FAP-001 pivotal trial and had the expertise, data quality standards, and sufficient patient population to conduct this trial. Based on this experience, the NCI and Pharmacia/Pfizer selected MDACC to design, implement, and coordinate the FAP phenotype suppression trial.

After the 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 young patients. To address this concern, a development plan that included both a Phase I (Pilot Toxicity / Methods Validation Study of Celecoxib in Genotype or Phenotype-Positive Children with Familial Adenomatous Polyposis, 10 to 14 years old) and a Phase III (Efficacy and safety in genotype positive-phenotype negative subjects with FAP, 10 to 17 years old) 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 (Pfizer), MDACC and NCI. A final protocol, that included 2 placebo subjects in each 6 subject cohort, was ready for institutional review board (IRB) submission in January 2002.

Because this study included pediatric patients, 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 Phenotype Suppression Study was initiated in December 2002. The last subject completed the study in late 2004 and the DSMB reviewed all of the safety data in detail in December 2004. Their detailed report concluded that the highest dose, 16mg/kg/d, was safe and the proposed phase III trial be allowed to proceed with that dose.

During the time the phase I was recruiting, Pharmacia/Pfizer was working actively on the Phase III protocol. In September of 2003 a meeting was held with experts in management of FAP to discuss the protocol design as well as give them an update on the Phase I study. This was followed with another meeting in February of 2004 to again discuss protocol design. At this time, Dr. James Church (The Cleveland Clinic) shared unpublished sigmoidoscopy findings that raised serious concerns about the availability of phenotype negative patients in the considered patient population. In May of 2004 the group met again to discuss:

1. A meaningful clinical endpoint for the new patient population.
2. The patient population and the incorporation of and definition of early phenotype.

3. Definition for the beginning of phenotype expression and the maximum number of polyps that can safely be removed at baseline and during subsequent visits.

In September of the same year another meeting (with participation of new international investigators) was held to discuss how to measure the primary endpoint. At the end of September 2004, Vioxx was withdrawn from the market and on December 17, 2004, information on the cardiovascular (CV) safety of celecoxib based on results from one of three long-term trials was made publicly available (NIH 2004). As a result, during the first part of 2005, regulatory agencies around the world initiated evaluations concerning the CV safety of COX-2 inhibitors.

In March of 2005, there was a teleconference with experts in the management of FAP to revise the protocol synopsis to be sent to the FDA. On March 24, 2005 the briefing document on the Phase III study design was sent to the FDA. On April 22, 2005 Pfizer along with the NCI presented the Phase III protocol design to the FDA. As a result of this meeting Pfizer submitted a request for special protocol assessment (SPA) of this protocol to the FDA on June 21, 2005.

On August 9, 2005, Pfizer received comments regarding the SPA from FDA. At this time, the Phase III protocol is in the process of being finalized. A first patient first visit date is estimated for January 2006.

Based on a 2-year recruitment period and 5-year study duration, the estimated date for completion of the study is 1Q 2013. However, there are several factors that may lead to recruitment extending beyond two years:

1. Potential impact of the COX-2 cardiovascular safety concerns on subject enrollment.
2. General difficulties associated with the enrollment of young patients in clinical trials.
3. Rate of screen failures may be greater than estimated due to the limited information on the disease characteristics in young FAP patients.

As can be observed from this sequence of events, finalizing a development plan that is acceptable to investigators, the NCI, the FDA, and Pfizer has proven to be complex. Detailed information regarding the timelines for interactions among the MDACC, the NCI, the FDA, and Pharmacia/Pfizer 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 study was discussed. In the December 23, 1999 accelerated approval letter, as part of the Subpart H commitment, the FDA and Pharmacia (Pfizer) 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 (Pfizer) began further development work on the registry protocol. In consultation with experts in the management of FAP, 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 yet been characterized; and as a consequence the information required to identify the historical control groups was not available. 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 (Pfizer) sought to develop an alternative strategy that would provide long-term safety and efficacy data. In January 2001, Pharmacia (Pfizer) submitted to the FDA a proposal for a trial that would be an alternative to the registry study. 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 an April 5, 2001 meeting with the FDA, this study design was rejected by the FDA as not providing direct data on the clinical benefit of celecoxib and not addressing long-term safety. While the FDA acknowledged the limitations of establishing a registry, the Agency considered this approach preferable.

In May 2001, Pharmacia (Pfizer) again continued planning for a registry study. 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 CGA for review in April 2002. However, upon further consideration, response to this protocol by the CGA was not positive due to concerns that data entry would be too labor intensive for health care providers, thereby limiting collection of data. Given these concerns, MDACC worked with Pharmacia (Pfizer) 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 (Pfizer) 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.

Following this, Pharmacia (Pfizer) focused on the development of a registry-based study protocol that incorporated the utilization of data merging techniques for the collection of data from the selected registries. A draft study protocol was sent to FDA for review in February 2003 and was subsequently presented to FDA during the ODAC meeting on March 13, 2003.

Since the March 13, 2003 ODAC meeting, Pfizer has pursued a number of activities to ensure compliance with this phase 4 commitment. Preliminary review of the draft study protocol by FDA concluded in the Agency's acceptance of the draft protocol on April 4, 2003 provided that the sponsor addressed a number of recommendations and concerns posed by FDA reviewers. On May 6, 2004, a final revised study protocol was submitted to FDA for review, with acceptance received on August 9, 2004.

In the 2nd Quarter of 2003, Pfizer designed an action plan with a focus on four main areas:

1. Identification of FAP registries meeting registry selection criteria (completed September 2003),
2. Selection of a Contract Research Organization –(CRO) to assure standardization of processes and procedures for data collection, verification, merging, and analysis (completed November 2003),
3. Finalization of study protocol after reaching investigators' consensus (final protocol submitted to the Agency on May 6, 2004) and,
4. Compliance with institutional regulatory requirements for approval of study protocol and study documents at each participating registry (completed at the U.S., Denmark and Canada Registry sites and ongoing in the Australia and Germany Registry sites).

As of December 2004, the study relied on active participation of 5-well established registries (David G. Jagelman Inherited Colorectal Cancer Registry at Cleveland Clinic, U.S.; Familiar GI Cancer Registry-Toronto at Mount Sinai Hospital, Canada; The Danish Polyposis Register-Copenhagen at Hvidovre University Hospital, Denmark; Duesseldorf FAP Registry at Heinrich Heine University, Germany and Victorian FAP Registry at The Royal Melbourne Hospital, Australia) with actual study initiation performed in September 1 and December 6, 2004 at the US and Danish registry sites, respectively.

In September 2004, Vioxx was withdrawn worldwide and on December 17, 2004, information on the cardiovascular (CV) safety of celecoxib based on results from one of three long-term prevention trials was made publicly available (NIH 2004). As a result, during the first part of 2005, regulatory agencies around the world initiated evaluations concerning the CV safety of COX-2 inhibitors (i.e., FDA Arthritis and Safety and Risk Management Advisory Committees Meeting, EMEA Article 31 Referral, Health Canada

Expert Advisory Panel Meeting on COX-2 Inhibitors and the Australian TGA's ADEC review process). These events were accompanied by the withdrawal of the FAP indication by Health Canada and by Pfizer's agreement to a temporary suspension of the launch of Onsenal® (celecoxib) indicated for the treatment of FAP in Europe until finalization of EMEA's assessment.

These regulatory actions have had a substantial impact on the level of activity in the FAP Registry Study, resulting in very limited progress observed in the current year. On March 15, 2005 the study was re-activated at the Cleveland Clinic Registry after being put on hold in December 2004. In May 2005, the Mount Sinai Registry in Toronto was initiated contingent upon enrollment of retrospective celecoxib-treated patients and historical/concurrent controls. More recently, in June 2005, the investigator at the Danish Registry, Professor Steffen Bülow, was given permission by the Danish Medicine Agency to prescribe Onsenal® on a per patient basis. Further activities are ongoing at the Australian and Germany sites to ensure compliance with all regulatory requirements.

Another important aspect that could influence the study aims and progress relates to difficulties in finding the necessary number of patients who would meet the study inclusion criteria and who would provide the required data to answer the study end-points. It is important to take into account the rarity of FAP (incidence ranges from 0.9 to 1.9 new cases per million inhabitants and prevalence rates range from 26.3 to 46.5 per million cases of affected persons with the disease at a given point in time) (Bülow 2003) when evaluating the progress of the study.

In addition, at this moment it is unclear what the level of impact from the cardiovascular safety reviews and the prominent and widespread media attention will be on the willingness of patients to accept celecoxib as part of their treatment. While this potential compliance issue may lessen over time, at this point its impact is difficult to evaluate and/or quantify in the short term. Taking all the above circumstances into account, it is expected that the number of patients and timelines committed for this study will not be reached as originally agreed. A timetable of events for interactions with Investigators/Institutions, CRO, and Regulatory Authorities performed by Pfizer in relation to this study commitment is outlined in Appendix 2 "Study Development Timetable" demonstrating Pfizer's due diligence in initiating this study.

6. STATUS POST-APPROVAL SUBPART H CLINICAL COMMITMENTS

6.1. Phenotype Suppression Trials

6.1.1. Phase I Pilot (Dose-Finding) Study

6.1.1.1. **Title:** *Phase I Pilot Toxicity / Method Validation Study of Celecoxib in Phenotype or Genotype-Positive Children with Familial Adenomatous Polyposis*

6.1.1.1.1. **Summary of Study Design**

6.1.1.1.1.1. **Study Sites**

University of Texas MD Anderson Cancer Center (MDACC), Texas Children's Hospital and Cleveland Clinic.

6.1.1.1.1.2. **Patient Population**

Eighteen adolescent (ages 10-14 years) phenotype positive or APC mutation positive carriers with non-surgical adenoma burden

6.1.1.1.1.3. **Primary Objective**

To establish a safe dose of celecoxib in adolescents (ages 10-14 years).

6.1.1.1.1.4. **Schema**

Patients were to be entered into 3 consecutive cohorts that received celecoxib 4 mg/kg/day, 8 mg/kg/day or 16 mg/kg /day (approximating 100 mg BID, 200 mg BID and 400 mg BID, respectively for patients > 50kg). In each cohort four participants were assigned to receive celecoxib and two participants were assigned to receive placebo. Treatment was to proceed for three months in each cohort. Unblinding was to be carried out following completion of each cohort treatment. If no dose-limiting toxicity (DLT) was observed in a cohort, dose escalation was to proceed in the subsequent cohort.

6.1.1.1.1.5. **Status**

1. Study Initiation: December 2002
2. First subject enrolled: December 16, 2002
3. Last Subject Enrolled: June 14, 2004
4. Study Completion: December 2004
5. Final Clinical Study Report: August 2005

6.1.1.1.1.6. Results

Randomization of cohort 1 began on December 20, 2002. The first patient on cohort 2 was randomized just over 6 months later on July 2, 2003. The last patient on cohort 3 was randomized on June 14, 2004. Of eighteen patients randomized, 15 (83%) were white, 2 were black, and 1 was Asian. Ten patients (56%) were female and all 18 patients had a median (range) age of 12.3 years (10.1 to 14.9). Overall, the median (range) time on study drug and time on study were 3.0 months (2.7 to 3.4) and 5.1 months (3.3 to 6.1), respectively.

Median months on drug for the placebo, 4 mg/kg, 8 mg/kg, and 16 mg/kg treatment groups were 3.0, 2.9, 3.1, and 2.9 months, respectively. All but one patient (4 mg/kg celecoxib in month 3) were 80% compliant and all patients completed therapy per protocol plan. Vital statistics were unremarkable and no trend with treatment was noted. Laboratory values by treatment group were classified as low, normal, and high based on age and gender adjusted criteria. Overall, 88% of all lab values fell in the normal range. Nine percent were classified in the low range and only 3% were classified as above normal. Differences by treatment were unremarkable. Overall, 24 adverse events, all grade 1, were reported by placebo treated patients. Among 4mg/kg treated patients, there were 22 grade 1 and 2 grade 2 adverse events reported. Seven adverse events, 5 grade 1 and 2 grade 2, were reported by patients treated with 8 mg/kg and all 21 adverse events reported by patients treated with 16 mg/kg of celecoxib were grade 1. Patient 2006, treated with 8 mg/kg celecoxib, reported no adverse events. Since no adverse event was attributed to any treatment, protocol guidelines the maximum tolerated dose recommended for subsequent phase II evaluation should be 16 mg/kg.

6.1.2. Phase III: Phenotype Suppression/Regression Trial

6.1.2.1. Title: *A Phase III Placebo-controlled Trial of Celecoxib in Genotype Positive Subjects with Familial Adenomatous Polyposis*

6.1.2.1.1. Summary of Study Design

6.1.2.1.1.1. Proposed Study Sites and Planned Sample Size

To date, there are 6 confirmed US sites of a planned 20 sites worldwide. The lead site is MD Anderson Cancer Center. Other countries that have confirmed participation are Brazil, Denmark, Germany, Italy, Israel, Netherlands, Poland, Spain and the UK. There are several countries that have yet to confirm their participation: Finland, France, South Africa and Sweden.

The target enrollment is approximately 200 patients (randomized in 1:1 ratio).

6.1.2.1.1.2. Patient Population

To be eligible for this trial, subjects must be 10 to 17 years old at the time of enrollment, have confirmed FAP genotype based on genetic predisposition testing and meet one of the following conditions:

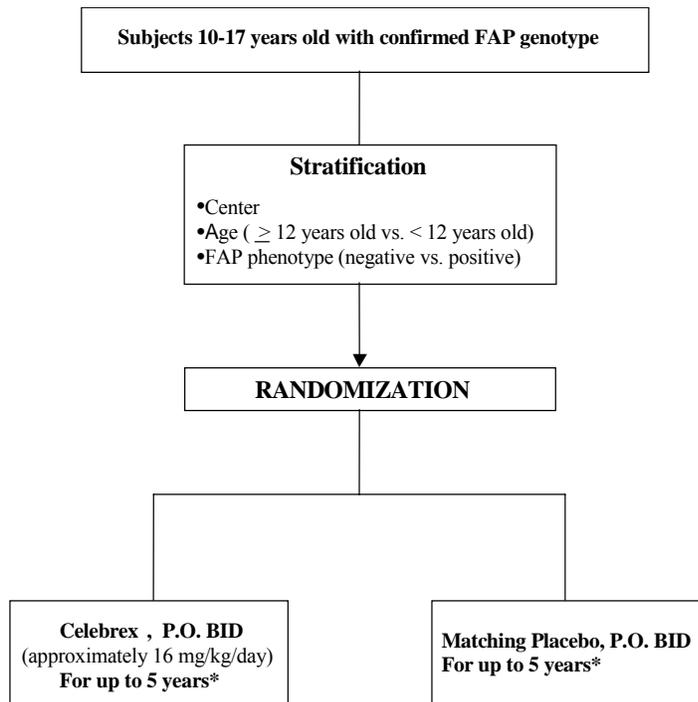
1. Have no visible colorectal polyps without dye enhancement (phenotypic negative FAP subject).
- or
2. Have < 20 colorectal polyps visible (>2mm, visible without dye enhancement). The polyps must be removed to render the colon polyp free and thus amenable to serial endoscopic surveillance (phenotypic positive FAP subject).

6.1.2.1.1.3. Primary Objective

To compare the time from randomization to treatment failure for subjects treated with celecoxib versus subjects treated with placebo, where treatment failure is defined as one or more of the following:

1. Appearance of ≥ 20 polyps at any colonoscopy during the study,
- or
2. A diagnosis of colorectal malignancy.

6.1.2.1.1.4. Schema



6.1.2.1.1.5. Status:

1. Study Initiation: ~1Q 2006
2. Estimated Study Completion: ~1Q 2013 – Based on a 2-year recruitment rate and 5-year study
3. Final Clinical Study report: ~ 4Q 2013

6.1.3. FAP Registry Study

6.1.3.1. Title: *A Registry-Based Observational Study Assessing Clinical Outcomes in Familial Adenomatous Polyposis in Patients Receiving Celecoxib (Celebrex®, Onsenal®) Compared with Control Patients.*

6.1.3.2. Summary of Study Design

6.1.3.2.1. Study Sites

In order to ensure availability of data for the required populations of historical control patients, the study is being conducted in the following countries where established FAP registries have been operational since 1991: United States, Canada, Australia, Denmark, and Germany. Participation of other countries is currently under consideration.

6.1.3.2.2. Patient Population

Two hundred celecoxib treated patients will be compared to matched patients within the database.

6.1.3.2.3. Endpoints:

6.1.3.2.3.1. Efficacy Measures

6.1.3.2.3.1.1. Primary

1. Time to FAP-related surgical events, specifically
 - a. Time to first excisional polypectomy post Ileorectal Anastomosis (IRA) of a rectal adenomatous polyp greater than or equal to 5mm. in size.
 - b. Time to first excisional polypectomy post Ileopouch Analanastomosis (IPAA).

6.1.3.2.3.1.2. Secondary

1. Time to first resectional or ablational event for rectal, colonic, pouch or duodenal adenomas that does not meet the primary outcome.
2. Time to FAP-related adverse event, defined as time to the first of any of FAP-related cancers, desmoids tumors requiring procedural intervention, hospitalizations or procedural interventions, 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).

3. Time to conversion from IRA to IPAA.
4. Duodenal adenoma burden as measured by Spigelman Stage and/or rectal or pouch adenoma burden based on polyp counts and sizes.

6.1.3.2.3.2. Safety Measures

All serious adverse events (both expected and unexpected) occurring while a patient is receiving celecoxib during his/her prospective participation in the study regardless of the apparent relationship to the drug.

6.1.3.2.4. Study Conduct and Monitoring:

Established national and regional FAP registries in selected countries will constitute the sources of data for the study. Available information indicates that demographic, clinical, surgical and pathological data from patients diagnosed with FAP are captured and updated regularly within the registries' databases. Most of the registries, however, have not systematically recorded data on the pharmacological treatments prescribed to patients but such data is readily available in the patient's medical record.

Data from patients participating in selected registries and meeting the eligibility criteria for study entry will be collected using the registries collection data frame (i.e. automated database) and by means of specifically designed case report forms (CRFs).

At baseline the following information will be obtained for eligible patients from each of the institutional registries databases:

1. Date of birth
2. Gender
3. General medical history (to the extent available)
4. Basis for diagnosis of FAP (including genotype, if performed)
5. Date of diagnosis of FAP phenotype
6. Diagnosis date and type of any prior FAP-related adverse events
7. Dates and types of prior endoscopies, abdominal computerized tomography (CT) scans or FAP-related surgical events
8. Extent of polyp burden (polyp counts and sizes) at time of prior endoscopies or FAP-related surgeries
9. Spigelman stage
10. Extent of desmoid formation on any CT scans
11. Starting date and starting dose of celecoxib for FAP (in celecoxib-treated group)

12. Pathology report

During the study follow-up period, the following information will be obtained from each of the institutional registries databases and from the study case report forms at 6-months intervals:

1. Diagnosis date and type of any FAP-related events
2. Dates and types of endoscopies, abdominal CT scans, or FAP-related surgical or ablational events
3. Extent of polyp burden (polyp counts and sizes) at time of endoscopies or FAP-related surgeries
4. Spigelman stage
5. Number of polypectomies at time of endoscopies
6. Extent of desmoid formation on any CT scans
7. Doses and duration of celecoxib therapy for FAP (in celecoxib-treated group)
8. Types and timing of any serious adverse events among celecoxib-treated patients
9. Pathology report
10. All serious adverse events (both expected and unexpected) occurring while a patient is receiving celecoxib during his/her prospective participation in the study regardless of the apparent relationship to the drug will be collected and evaluated.

No safety information will be actively searched for among the celecoxib-treated patients whose data will be collected in a retrospective manner (i.e., patients included in FAP registries in countries where the use of celecoxib for FAP has been approved since the year 2000). However, if at the time of review of these patients' original source of data (i.e., patients' medical records) for the collection of efficacy information, any of the Pfizer designated study personnel (i.e., registry coordinator and/or Clinical Research Organization-CRO-monitor) encounters that a serious adverse event (SAE) had occurred while a patient was receiving celecoxib, this event will be reported as a SAE.

Patients will be followed for up to 5 years. Study data will be extracted from the institutions' registries at 6-month intervals. Yearly study report updates are foreseen. Study patients will include patients receiving treatment with celecoxib (as per local labeling instructions) and concurrent patients not treated with celecoxib. In addition, data from historical controls (FAP patients from whom data is available in the institutional registries databases from 1991 and who were not treated with celecoxib) will be obtained from each of the registries' databases after confirmation of the required matching criteria.

6.1.3.2.5. Statistical Plan

The primary efficacy endpoint, time to FAP-related surgical events, will be examined with life table or Kaplan-Meier methods, as appropriate. Comparisons between celecoxib patients and matched historical/concurrent controls will be performed using a log-rank test.

The study is not powered to find statistically significant differences between the celecoxib group and the matched control group in time to FAP related events. However, the study is large enough to detect trends. For the protocol a ‘strong trend’ is defined as a p-value of less than 0.10 and a ‘weak trend’ as a p-value of less than 0.15. In addition to the above “definition of trends” that will help to guide the interpretation of results, final evaluation of findings will also be based on clinical considerations related to the clinical impact/relevance of the study results. The table below lists the power of detecting either a strong trend or a weak trend when the true median effect is 3.75 years to 4.5 years for the celecoxib group and the control group median is fixed at three years.

Table 1: Power Estimation with 200 Patients in Each Treatment Arm Using One-Sided Test to Detect A Difference* in Time to First FAP-Related Event.

Significance Level	Hazard Ratio	Median Time in Years Celecoxib Group	Power
0.10	1.25	3.75	75%
	1.30	3.90	84%
	1.50	4.50	98%
0.15	1.25	3.75	82%
	1.30	3.90	89%
	1.50	4.50	>99%

* Assuming the median time in the control group is 3 years

6.1.3.2.6. Status

1. Date of Initiation: September 1, 2004
2. Current Number of Patients Contained in Registry: 16 patients and 1 matched control.
3. Estimated Study Completion: The original timeline for study completion was December 2009. However, due to issues outlined in this briefing document is expected that the study will not be completed within the expected timelines and reassessment of the target date for study completion is currently required.

7. CONCLUSION

FAP is a rare disease but is associated with the highest possible risk (100%) of developing malignancy. With a clearly identifiable IEN lesion (colonic polyps), there is an opportunity to develop pharmacological therapies at targets like COX-2 that are expressed early in the carcinogenic process especially in gastrointestinal IEN and malignancy.

Pfizer, in collaboration with the NCI, is developing celecoxib as a therapy for FAP patients. Celecoxib has been widely studied and used in patients with arthritis, thus providing a large database of safety information that would not be achieved from the FAP population alone. Development of celecoxib for the treatment of FAP is challenging due to disease rarity, and it is difficult to identify enough patients that have received uniform (surgical) therapy. A global coordinated approach has been required to maximize patient inclusion.

Pre-clinical and clinical evidence supports COX-2 as a therapeutic target in gastrointestinal neoplasia. Clinical evidence has also shown that non-selective COX inhibition can reduce polyps. This led to the first study of celecoxib in FAP patients. This randomized double-blind placebo controlled study demonstrated a statistically significant 28% reduction in the number of polyps in patients taking 400mg BID over 6 months compared to 4.5% in patients receiving placebo.

Further research to evaluate the longer-term therapeutic value of celecoxib will focus on two broad patient populations. First, patients with early FAP disease, before surgical intervention, will be enrolled a phase III placebo-controlled Trial of Celecoxib in Genotype Positive Subjects with Familial Adenomatous Polyposis. Celecoxib or placebo will be given over 5 years. Second, patients with established FAP disease are being enrolled in a registry-based observational case control study that will assess clinical outcomes in patients receiving celecoxib for longer than 6 months compared with historical control patients from the same registry. This study is aiming to recruit 200 celecoxib patients and 200 control patients and requires FAP community registries to be established long enough to provide historical controls. This study was initiated on September 1, 2004.

In summary, COX-2 is a potentially significant therapeutic target in patients with FAP, a population that is at the highest risk of developing cancer. If the challenges of drug development in this rare disease can be overcome, then the clinical benefit and safety of celecoxib will be demonstrated both in FAP patients who have already had surgical intervention and in patients with early FAP before surgical intervention.

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APPENDIX 1

A Phase I Pilot Toxicity / Methods Validation Study of Celecoxib in Genotype-Positive Children with FAP” (NCI Contract N01-CN05126 / M.D. Anderson Protocol ID02-090)

STUDY DEVELOPMENT TIMETABLE

DATE	ACTION
April 2000	MDACC filed “Intent to Submit Study Proposal” to NCI, Division of Cancer Prevention
June 2000	MDACC submitted technical and business proposals to NCI
August 2000	NCI review of proposals completed Review sent to MDACC MDACC submitted responses to NCI request for additional information concerning business and technical proposals
September 2000	MDACC files additional business information with NCI
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	Pharmacia reviews protocol
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 and to Pharmacia
March 2002	MDACC Clinical Research Committee reviewed and approved protocol MDACC IRB approved protocol
April 2002	CRF development and review with collaborators
May 2002	MDACC initiated collection of regulatory documents & submitted to CCS Associates, Inc.
May 2002	MDACC received NCI approval for activation of protocol

DATE	ACTION
June 2002	<p>MDACC Office of Research Administration issues memo formally approving protocol and guidelines for activation</p> <p>Additional CRF responses received</p> <p>Pharmacia submits “Supported Trial Agreement” to MDACC</p> <p>Site initiation meeting held at MDACC – Pharmacia informs team that there are difficulties with the stability of the Celecoxib orally dispersible tablet formulation</p> <p>Meeting held with Phase II study collaborators at St. Mark’s Hospital in Harrow</p>
July 2002	<p>Cleveland Clinic Foundation submits protocol to their IRB</p> <p>Pharmacia review of protocol revisions suggested at site initiation held on 25 June 2002 received at MDACC</p> <p>Texas Children’s Hospital submits protocol to their IRB</p> <p>Executed “Supported Trial Agreement” returned to Pharmacia by MDACC</p>
August 2002	<p>Texas Children’s Hospital IRB approves protocol</p> <p>Protocol revised – Celecoxib orally dispersible tablet “formulation not available for this study</p> <p>Pharmacia signature pages for protocol dated 11 February 2002 and 16 August 2002 received</p> <p>Protocol sent to MDACC IRB and to Pharmacia</p>
September 2002	MDACC IRB approves protocol
November 2002	NCI approves protocol
December 2002	First patient randomized to protocol
October 2004	Last Patient Last Visit
December 2004	DSMB reviews data and recommends the Phase III proceed with the 16mg/kg/day dose

*A Phase III Placebo-controlled Trial of Celecoxib in Genotype Positive Subjects with
Familial Adenomatous Polyposis*

STUDY DEVELOPMENT TIMETABLE

DATE	ACTION
December 2002	First Patient Enrolled in Phase I study
September 2003	Protocol design meeting with experts in the management of FAP
February 2004	Meeting with experts- the unavailability of phenotype negative patients
May 2004	Meet with experts - clinical meaningful endpoint discussed
June 2004	Last patient enrolled in the Phase I study
September 2004	Meet with experts - discussion how to measure the endpoint
December 2004	DSMB of Phase I study meets for safety review and concluded the 16mg/kg/day dose was safe FDA reviews cardiovascular (CV) Safety of Cox-2 inhibitors EMA initiates review of CV safety of COX-2 inhibitors
January 2005	Pfizer agrees to a temporary suspension of launch of Onsenal® (celecoxib) indicated for the treatment of FAP in Europe until finalization of EMA's assessment
February 2005	Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss overall risk/benefit of COX-2 inhibitors
March 2005	Teleconference with experts to design appropriate phase III trial Submission of revised briefing package with proposed study to FDA
April 2005	Meeting with FDA to present the Phase III protocol design
June 2005	Request for Special Protocol Assessment (SPA) for Phase III protocol submitted to FDA
July 2005	Revised labeling for Celebrex® reflecting cardiovascular safety information approved by FDA
August 2005	Comments from FDA regarding SPA received by Pfizer
Presently	Completion of final protocol and planned IRB reviews ongoing
November 2005	Revised EU Labeling for Onsenal® (celecoxib) FAP
January 2006	Estimated First Patient Enrolled
January 2013	Last Patient Last Visit (assuming a 2 year enrollment and 5 years therapy)

APPENDIX 2:

A Registry-Based Observational Study Assessing Clinical Outcomes In Familial Adenomatous Polyposis In Patients Receiving Celecoxib (Celebrex®, Onsenal®) Compared With Control Patients

STUDY DEVELOPMENT TIMETABLE

DATE	ACTION
December 1999	FDA grants accelerated approval for celecoxib in FAP
February 2000	Discussion with experts initiated
December 2000	Submission of alternative proposal to FDA
April 2001	Pharmacia meets with FDA to propose alternate controlled study of celecoxib vs. DFMO. FDA reiterates its desire for a registry study
May 2001	Pharmacia contacts MDACC for protocol development and for establishing network with Collaborative Group of the Americas on Inherited diseases (CGA)
June 2001	MDACC confirms interest in setting up Registry, with grant from Pharmacia
August 2001	MDACC send copy of registry proposal written in 6/2000, which is basis for current proposal Pharmacia sends comments regarding protocol endpoints to MDACC Pharmacia provides ID 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 study
April 2002	Site map for Registry sent to Pharmacia. Protocol was sent to CGA members for review. Budget proposed to Pharmacia by MDACC
July 2002	Budget approved by Pharmacia. 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 Pharmacia
November 2002	Prototype web site scheduled for November 23, 2002
December 2002	Web-based Study prototype sent to Pharmacia. Submitted to MDACC IRB for approval
January 2003	MDACC IRB rejects web-based registry protocol
February 2003	Revised registry-based protocol under development
March 2003	Draft Study protocol submitted to FDA for review

DATE	ACTION
April 2003	Under preliminary review, FDA finds draft Study protocol acceptable and recommends submission of detailed protocol once formal agreements with registries are reached
September 2003	First Investigator Meeting - FAP Registry Planning Meeting to review draft protocol and obtain input prior to finalization of Study protocol for health authorities review
September to November 2003	Pfizer interviews six CROs to provide service on study conduct and monitoring.
December 2003	Bid adjudicated to CRO-Quintiles
February 2004	Pfizer and Quintiles Study Kick-Off Meeting
April 2004	U.S. Informed Consent template finalized Final protocol of the Registry-based Observational study approved and signed-off internally by Pfizer
May 2004	Final protocol submitted to FDA for review IRB approval received from Cleveland Clinic
June 2004	Contract with CRO-Quintiles executed to perform Project Management, Data Management, Programming, Monitoring, Maintaining Trial Master File, Biostatistics and Medical Writing for the Registry Study IEC approval from Hvidovre Univ. Hospital Non-U.S. Informed Consent template finalized
July 2004	Assessment visit performed by Quintiles and Pfizer at Cleveland Clinic to review David G. Jagelman Inherited Colorectal Cancer Registries database content and structure Study contracted executed with The Cleveland Clinic, U.S.
August 2004	CRF finalized to capture Medical History and celecoxib treatment, if data is not captured at Institution's Registry
September 2004	Site Initiation Visit performed at Cleveland Clinic, and site activated IEC approval from Heinrich-Heine-Universitat, Dusseldorf Assessment visit performed by Quintiles and Pfizer at Hvidovre Univ. Hospital to review The Danish Polyposis Register-Copenhagen database content and structure Study Kick-off Meeting in Prague to review overall study (protocol, SAE reporting, semi-annual data transfer, monitoring, etc.)
October 2004	IEC approval from The Cancer Council of Victoria Registry-based Observational study protocol was amended (Amendment #1) due to further comments received by the investigators during the Kick-off Meeting. No revisions to the informed consent form were necessary.

DATE	ACTION
November 2004	<p>Study contract executed with Hvidovre University Hospital, Denmark</p> <p>Cleveland Clinic IRB approves Protocol Amendment #1</p> <p>Revision of CRO-Quintiles contract to include additional service by Quintiles for investigator contract negotiation and payment administration</p> <p>First data transfer received from Cleveland Clinic</p> <p>Amendment #1 protocol submitted to FDA</p>
December 2004	<p>Site Initiation Visit performed at Hvidovre Univ. Hospital, and site activated</p> <p>First data transfer received from Hvidovre Univ. Hospital</p> <p>Information on the cardiovascular (CV) safety of celecoxib based on results from two long-term cancer trials publicly released. Health Canada withdrew FAP indication.</p> <p>Cleveland Clinic investigator withholds Study</p> <p>First Study semi-annual report submitted to EMEA</p> <p>Mt. Sinai IRB approves Protocol Amendment #1</p>
January 2005	<p>Pfizer agrees to a temporary suspension of launch of Onsenal® (celecoxib) for the FAP indication in Europe until finalization of EMEA' assessment</p> <p>U.S. Informed Consent template revised to include further information on CV risk</p> <p>Non-U.S. Informed Consent template revised to include further information on CV risk</p>
February 2005	<p>Mount Sinai IRB approves revised informed consent form</p> <p>Cleveland Clinic IRB approves revised informed consent form</p>
March 2005	<p>Study re-activated at Cleveland Clinic Registry after being put on hold in December 2004</p>
April 2005	<p>Study contract executed with Mount Sinai, Canada</p>
May 2005	<p>Combined Assessment and Site Initiation Visit performed by Quintiles and Pfizer at Mount Sinai to review Familial GI Cancer Registry-Toronto. Site activated contingent upon enrollment of retrospective celecoxib-treated patients and historical/concurrent controls</p>
June 2005	<p>Danish Registry investigator, obtains permission from the Danish Medicine Agency to prescribe Onsenal® on a per patient basis</p> <p>Second Study semi-annual report submitted to EMEA</p>
September 2005	<p>Ongoing contract negotiations with Heinrich-Heine-Universitat, Germany</p>

DATE	ACTION
November/ December 2005	Combined Assessment and Site Initiation Visit to be performed by Quintiles and Pfizer at Heinrich-Heine-Universitat, Germany to review Dusseldorf FAP Registry
December 2005	2005 Annual Report to be submitted to FDA Third Study semi-annual report to be submitted to EMEA
June 2006	Fourth Study semi-annual report to be submitted to EMEA
December 2006	2006 Annual Report to be submitted to FDA Fifth Study semi-annual report to be submitted to EMEA
March 2006	Perform combined Assessment and Site Initiation Visit by Quintiles and Pfizer at The Cancer Council of Victoria, Australia to review Victorian FAP Registry
June 2007	Sixth Study semi-annual report to be submitted to EMEA
December 2007	2007 Annual Report to be submitted to FDA Seventh Study semi-annual report to be submitted to EMEA
June 2008	Eighth Study semi-annual report to be submitted to EMEA
December 2008	2008 Annual Report to be submitted to FDA Ninth Study semi-annual report to be submitted to EMEA
June 2009	Tenth Study semi-annual report to be submitted to EMEA
December 2009	Final Study Report (contingent upon completion of enrollment)