A DOUBLE-BLIND, RANDOMIZED, PHASE III TRIAL OF THE SAFETY AND EFFICACY OF CPP-1X / SULINDAC COMPARED WITH CPP-1X, SULINDAC AS SINGLE AGENTS IN PATIENTS WITH FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

CPP FAP-310

CPP-1X (Eflornithine HCl)

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Sponsored by

Cancer Prevention Pharmaceuticals, Inc.

1760 E. River Road, Suite 250

Tucson, AZ 85718

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INVESTIGATOR PROTOCOL AGREEMENT

CPP FAP-310

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By signing below, I agree:

1. That my staff and I have read, understand and will adhere to the protocol as written and agree that any changes to the protocol will be agreed to and approved by Cancer Prevention Pharmaceuticals, except to eliminate an immediate hazard to the patients. Prior to instituting changes, I will obtain approval from the Independent Ethics Committee (IEC)/Institutional Review Board (IRB)/Research Ethics Board (REB);
2. To abide by all obligations stated on the FDA Form 1572 and other documents required by regulation;
3. To conduct this study in accordance with the current International Conference on Harmonization (ICH) guidance, the Good Clinical Practices (GCP) guidance the US FDA regulations, EMA regulations, Health Canada regulations, local competent authority regulations, and local IRB/IEC/REB and legal requirements;
4. To obtain IRB/IEC/REB approval of the protocol, any amendments to the protocol, and periodic re-approval as required, and to keep the IRB/IEC/REB informed of adverse events and periodically report the status of the study to them;
5. To ensure that each patient enrolled into the trial, or legally authorized representative has read and understands the current patient information, and has signed the Informed Consent form;
6. To ensure that I and all persons assisting me with the study are adequately informed and trained about the investigational drug and of their study related duties and functions as described in the protocol;
7. To make prompt reports of Serious Adverse Events (SAEs) and deaths as defined in the protocol, the FDA regulations, EMA regulations, local competent authority regulations, and Health Canada regulations;
8. To prepare and maintain adequate and accurate case histories to document all observations and other data pertinent to the study on each individual enrolled in the clinical trial.

Investigator Signature: _____ _____

Date

Investigator Name (Print): _____

Institution: _____

_____

_____

1. GENERAL INFORMATION

1.1. Protocol Title

A Double-Blind, Randomized, Phase III Trial of the Safety and Efficacy of CPP-1X/Sulindac Compared with CPP-1X, Sulindac as Single Agents in Patients with Familial Adenomatous Polyposis (FAP)

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Molecular MD Inc., 1341 SW Custer Drive, Portland OR, 97219, USA, will perform the testing for the pharmacogenomic samples collected

inVentiv Health Clinique, Inc., 2500 rue Einstein Street, Québec City, Québec G1P 0A2, Canada, will perform the bioanalysis for the pharmacokinetic samples collected.

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Chief Medical Officer

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1.6. Study Schema

MAJOR ELIGIBILITY CRITERIA

1. Diagnosis of Familial Adenomatous Polyposis (FAP) with confirmed APC mutation AND age ≥ 18 years.
2. If prior colorectal surgery, at least 3 years since colectomy/proctocolectomy with ileo-rectal anastomosis (IRA) or pouch.

Disease at One or More of These Sites

1. Intact colon (pre-colectomy) 2. Rectal/Pouch Polyposis 3. Duodenal Polyposis

Stratification

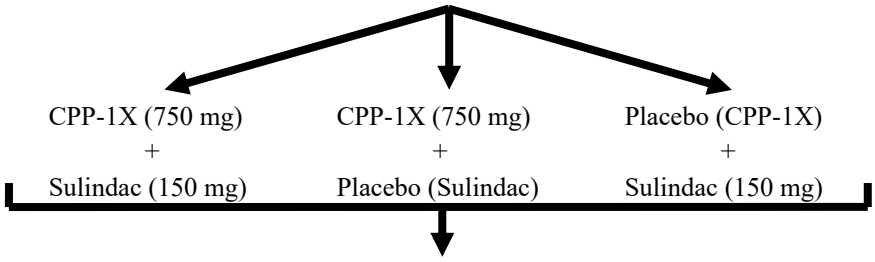
Stratification based on FAP-related time to first event prognosis.

1. best (i.e., longest projected time to first FAP-related event) – rectal/pouch polyposis
2. intermediate – duodenal polyposis
3. worst – pre-colectomy

If a subject has two or more of these disease sites, the stratum for randomization will be according to the most severe prognosis stratum as defined above.

Randomization

A total of 150 subjects, drugs are taken once daily.



Randomized subjects will receive 24 months of treatment and complete their final assessment or come off-study for an FAP-related event or for other reasons (for example, safety issues, non-compliance, withdrew consent, lost to follow-up).

Subjects completing 24 months of treatment without an FAP-related event may continue on treatment for up to 48 months based on their randomization date as follows:

1. If randomized between November 2015 and April 2016 eligible for up to 36 months of treatment
2. If randomized between May 2015 and October 2015 eligible for up to 42 months of treatment
3. If randomized between July 2014 and April 2015 eligible for up to 48 months of treatment

or until one of the following occurs:

1. Subject has an FAP-related event or comes off study for other reasons
2. Trial end-date of April 30, 2019 has been reached
3. 90 FAP-related events have occurred
4. Less than 90 FAP-related events have accrued prior to April 30, 2019 and an earlier trial end-date has been set by the Sponsor and reviewed by the DMC
5. An earlier trial end date prior to April 30, 2019 has been recommended by the DMC for safety reason and approved by the Sponsor

2. BACKGROUND INFORMATION

2.1. Natural History, Current Surgical and Endoscopic Treatment

Familial Adenomatous Polyposis (FAP) is a syndrome caused by mutations in the Adenomatous Polyposis Coli (*APC*) tumor suppressor gene and propagated by an autosomal dominant mode of inheritance. Details of this syndrome can be found at OMIM ®, (Online Mendelian Inheritance in Man), http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=175100, which is an authoritative listing of human genes and genetic phenotypes. This database is available to users' courtesy of NCBI, the National Center for Biotechnology Information.

FAP is caused by mutations/deletions in the *APC* gene, which is located on chromosome 5q21-q22. Gardner syndrome is a variant of FAP in which desmoid tumors, osteomas, and other neoplasms occur together with multiple adenomas of the colon and rectum (http://www.cancer.gov/cancertopics/pdq/genetics/colorectal/HealthProfessional/page4/AllPages).

Most FAP patients will have hundreds to thousands of colorectal adenomas, and without prophylactic surgery develop colorectal cancer before the age of 40. Prophylactic surgery may involve total abdominal colectomy with ileal-rectal anastomoses (IRA), accompanied by frequent rectal surveillance with polypectomy and cautery/laser ablation as needed. Patients with extensive rectal involvement undergo total proctocolectomy with ileal pouch-anal reconstruction.

Despite removing the main at-risk organ, many patients develop duodenal neoplasia (bulky adenomas/cancer) and require additional localized or Whipple radical surgery. The Spigelman classification (Stage 3 or 4)[1] can accurately predict those with adenomas that are most likely to progress to cancer. Bulow and colleagues[2] reviewed duodenal polyposis issues in FAP patients. Gastric antral adenomas may occur and rarely are symptomatic or progress to cancer.

Despite total proctocolectomy with ileal pouch reconstruction, approximately 50% of patients will develop adenomatous lesions in the neo-rectum.[3-6] There are case reports of cancer developing in the pouches. All patients who have a residual rectum after total colectomy require frequent surveillance, polypectomies and ablations for continuing rectal polyposis.

Desmoids are "benign tumors" (myofibroblastic) and cause significant morbidity and mortality in some patients. They are not associated with any specific FAP genotype but are more common if the APC mutation is distal to codon 1444; the major clinical risk factors are family history and prior colectomy. Women are at greater risk. Growth of these lesions, particularly when they involve the root of the mesentery, can lead to extensive surgery, often resulting in resection of ileal pouches and permanent ileostomy. Current treatment involves surgery, radiation, NSAIDS and anti-estrogens. None of these approaches have major impact on the growth of these lesions.[7-9] Although an important site of disease and morbidity for FAP patients, this protocol will focus on intestinal polyposis only.

Vasen and colleagues[10] provide evidence-based guidelines for the evaluation and management of FAP patients and provides detailed natural history data.

After prophylactic colectomy, all FAP patients undergo regular surveillance intervention, with proctoscopy and upper GI endoscopy every 6-12 months. Surgical intervention may be required for progressive FAP related disease (defined in protocol). We believe that disease control with our combination regimen will delay the occurrence of clinically meaningful events.

2.2. Pharmacologic Clinical Trials in FAP Patients

In the general population, certain types of colorectal polyps have increased risk of progression to colorectal cancer. High risk polyps (polyps with villous histology, size ≥1 cm, high grade

dysplasia, or multiple adenomas defined as 3 or more) have become the focus of colorectal tumorigenesis research due to the higher rate of malignant potential for these.[11-15] The biology of common colorectal cancer is similar to the FAP phenotype. Wallace and Lynch[16] summarized the current status of chemoprevention in FAP patients. The key drugs/drug combinations are described below.

2.2.1. Sulindac Alone

Labayle and colleagues[17] studied 10 FAP patients with IRA in a randomized placebo controlled double blind trial of sulindac 300 mg a day for 4 month intervals. In rectal assessment of polyp counts, there was a statistically significant reduction with sulindac compared to placebo (despite the small number of evaluable patients assessed).

Nugent[18] evaluated sulindac at 200 mg twice a day in 24 patients with duodenal neoplasia and in this group 12 had an IRA and the rectum was also evaluated. This was a placebo controlled randomized trial. Benefit was demonstrated in the rectum, but treatment was not statistically beneficial in the duodenum.

Giardello and his group[19] performed a randomized double blind trial in non-operated FAP patients or those who had an IRA. Sulindac at 150 mg twice a day was the treatment regimen. Rectal polyp numbers decreased 56% in the treated group.

Tonelli *et al.,*[20] studied 15 FAP patients after IRA. This non-randomized trial used sulindac 100 mg twice a day. A benefit was seen after 6 months, but not long-term.

Cruz-Correa[21] studied 12 patients post IRA for rectal polyp control with 150 mg of sulindac twice a day. A major reduction in polyp numbers was demonstrated, but with a 50% incidence of gastrointestinal erosions.

Giardiello and colleagues[22] utilized sulindac in 41 non-operated FAP patients, mean age of 13. By the end of the study all but 3 of the 21 subjects randomized to the sulindac arm were receiving 150 mg of sulindac daily twice a day. Treatment with sulindac for a four-year period was well tolerated. Few adverse events were reported and 93% were grade 1 or grade 2 and included leukopenia, photosensitivity, rash, urticaria, diarrhea, vomiting, bleeding, hyperbilirubinemia, blurred vision, abdominal pain, and influenza like syndrome. One subject was withdrawn because of possible drug-induced neutropenia. The incidence of any adverse event did not differ significantly between the sulindac group and the placebo group. There was no demonstrable difference in the adenoma formation compared to placebo.

2.2.2. Celecoxib Alone

Although FDA approved celecoxib for the treatment of FAP patients in 1999, Pfizer withdrew the agent's registration. Of note, this agent did not become a usual part of standard care for these patients. This is partly due to concerns for patient safety resulting from colorectal adenoma prevention studies reported in 2006.[23,24] These studies identified a small but finite risk of serious cardiovascular events associated with celecoxib treatment.

Albeit the one most prominent study was performed at MD Anderson, Houston, TX and St. Mark's Hospital, London.[25,26] Patients were randomized to placebo control, celecoxib 100 mg twice daily, and celecoxib 400 mg twice daily. In the Steinbach report,[25] 6 months of celecoxib, 400 mg twice daily showed a 28% change from baseline in the mean number of rectal polyps, the lower dose of the drug (100 mg twice daily) showed an 11.9% change in the mean number of polyps compared to baseline. Similar data were found in the duodenal cohort. Polyp reduction with small baseline tumor burden was only 14.5%, but 31% in more involved baseline duodenal adenomatosis. Again, effect was noted only in the high dose celecoxib patients. Sixty-eight

percent (68%) of patients in the placebo group, 56% of patients in the 100 mg twice daily group, and 57% of patients in the 400 mg twice daily group reported one or more adverse events of grade 2 or higher (NCI CTC, Ver. 3.0). The most common events were diarrhea and abdominal pain.

2.2.3. NSAIDs Plus Eflornithine Combination

This research program was activated in 2002, as a randomized Phase II study (ClinicalTrials.gov NCT00033371) comparing the effectiveness of celecoxib +/- eflornithine in FAP. Accrual was discontinued after approximately 111 patients were entered.[27,28] _ENREF_26

The stated purpose of this study was to "compare the effectiveness of celecoxib with or without eflornithine in preventing colorectal cancer in patients who have familial adenomatous polyposis". The outcome measures involved changes in polyp numbers, polyp burden, and plaque-like duodenal polyps after 6 months of treatment. This was a two-arm trial:

1. Oral celecoxib (400 mg) twice daily with oral eflornithine (500 mg/m^2), once daily, vs.
2. Oral celecoxib twice daily and oral placebo once daily

The major conclusions from that study were:

- Addition of eflornithine, at an average daily dose of 750 mg (three 250 mg tablets) to celecoxib did not significantly reduce raw adenoma count according to primary endpoint measure (polyps in reference cluster in still color photos) compared to celecoxib alone.
- At least borderline significance of the combination was achieved by secondary measures (counts in photos, weighted by diameter, and by video of larger segments of colorectum).
- No deleterious ototoxicity due to eflornithine was detected.
- No significant treatment-related adverse events were noted in either arm of the trial.
- Finding of greater effect on diameter-weighted burden suggests these agents may have greater effect at level of adenoma promotion than initiation.
- Based on findings from another trial, use of a web-based quantitative tool for capturing diameter-weighted adenoma counts from videos of total colon or rectum may be more informative than approaches to adenoma quantification to date.

2.2.4. Eflornithine Alone

There are extensive preclinical studies in mouse models of FAP. These mouse models express a mutant form of the mouse homolog of the human adenomatous polyposis (APC) gene. When these mouse models of FAP are treated with eflornithine alone, the agent causes a dose-dependent decrease in the number of both intestinal and colonic polyps.[29-31]

There have been no clinical trials in FAP patients using eflornithine alone although other clinical trials of eflornithine have shown suppressed tumor growth in multiple tumor types. As indicated above, the Lynch trial provides the first evidence of effect of eflornithine, at an average daily dose of 750 mg in patients with FAP.[28] There was no eflornithine alone arm in that trial, so the data only addresses eflornithine in combination with celecoxib. However, in that trial there was evidence for both safety of eflornithine at 750 mg/day in this patient population (no difference between NSAID alone and the combination arm) and efficacy (statistically significant effect of combination versus NSAID alone arm) for both total polyp volume and global polyp burden measures.

The major evidence for benefit of eflornithine derives from prospective, randomized, placebo-controlled clinical trials of eflornithine alone in patients with elevated risk for developing certain forms of cancer. In one trial of 81 men with a family history of prostate cancer, oral eflornithine alone (500 mg per day for one year) reduced prostate polyamine contents, prostate volumes and

prostate specific antigen (PSA) doubling times in men, compared to these same parameters in men taking placebo tablets.[32] In a second study, 291 people with prior non-melanoma skin cancers were treated with eflornithine alone (500 mg/m^2 per day for 4-5 years). In that study, the treatment with eflornithine was associated with a highly statistically significant reduction in metachronous basal cell skin cancers.[33] Toxicities were rare in both of these studies, and consisted of infrequent clinically non-significant ototoxicity (meaning that the ototoxicity was not apparent to the patient and was only detectable by quantitative audiology testing). A recent report of this eflornithine-related toxicity was reported in detail for a clinical trial evaluating the combination of eflornithine and sulindac.[34] Clinical studies of eflornithine monotherapy have also been conducted with trial endpoints consisting of tissue polyamine contents. These markers are dependent on ornithine decarboxylase (ODC), the eflornithine target protein. Doses, such as those proposed by the Sponsor, have been shown to reduce rectal mucosal tissue polyamine contents in a randomized placebo-controlled clinical trial.[35] This marker study is especially relevant to patients with familial adenomatous polyposis (FAP), where the target tissues include intestinal and colonic mucosa.

These clinical trial results are corroborated by clinical translational studies that are based on molecular epidemiology investigations. Examples of this type of evidence include studies replicated by three independent groups in humans showing that a polymorphism affecting the expression of ODC, the eflornithine target protein, is highly associated with metachronous colon adenomas[36,37] and sporadic breast cancer[38] In addition, two independent groups have reported that this same polymorphism is associated with prostate cancer[39] and colon cancer survival.[40]

2.3. Sulindac and Eflornithine; Colorectal Polyp Chemoprevention

Meyskens and colleagues[41] performed a Phase III double-blind trial involving resected sporadic adenoma patients treated for three (3) years with eflornithine (500 mg once a day) plus sulindac (150 mg once a day) compared to placebo/placebo that demonstrated a marked reduction (70%) of metachronous adenomas overall, 92% efficacy against advanced adenomas, and 95% efficacy in decreasing the risk of developing multiple adenomas compared to placebo. Additionally, this combination regimen was generally well-tolerated.

2.4. Biology Of Eflornithine

Ornithine decarboxylase (ODC) is a transcriptional target of the MYC oncoprotein and *MYC* transcription is suppressed by the *APC* gene product.[42,43] ODC enzyme activity and polyamine contents are elevated in the apparently normal colonic mucosa of genotypic FAP patients, compared to FAP normal family members.[44] These mechanistic and translational studies in humans indicate that ODC enzyme activity is up-regulated in the intestinal and colonic mucosa of patients with FAP.

Eflornithine, also known as DFMO, is an enzyme-activated, irreversible inhibitor of ODC, an essential enzyme in the polyamine synthesis pathway.[45] Studies in animal models of FAP indicate that eflornithine alone is effective in reducing the number of intestinal[29] and colonic[30] tumors. Eflornithine works in combination with the non-steroidal anti-inflammatory drug (NSAID) sulindac to further reduce tissue polyamine contents, as sulindac activates polyamine export mechanisms.[46] Combination treatment with eflornithine and sulindac dramatically reduce the incidence of metachronous colorectal adenomas in patients with prior sporadic adenomas.[41] The majority of sporadic colorectal adenomas have mutations in APC or another gene in the WNT signaling pathway. In addition, combinations of eflornithine and NSAIDS have been shown to reduce the number of advanced adenomas by more than 90% in mouse models of

FAP.[31] These results provide strong rationale that patients with FAP should respond to this therapy.

2.5. Rationale for Eflornithine Dose

Prior pharmacokinetic (PK) studies had documented linearity of serum eflornithine levels with oral doses as low as 100 mg/m^2/day.[47] Dose-de-escalation studies identified oral daily doses of eflornithine, which irreversibly inhibits an essential enzyme in polyamine synthesis pathway, in the range of 200-400 mg/m^2/day as a dose range that effectively reduced colorectal tissue polyamine contents.[35] Oral doses in this range achieve serum concentrations that inhibit ornithine decarboxylase enzyme activity and polyamine synthesis in cell culture models.[48] Based on these findings, a Phase III clinical trial of eflornithine combined with the non-steroidal anti-inflammatory drug (NSAID) sulindac was conducted to evaluate the effect of this combination on the incidence of metachronous colorectal adenomas in patients with prior sporadic (non-genetic) colorectal polys.[41] Based on an average adult body surface area of 1.6 m^2,[49] a dose of 500 mg oral daily dose of eflornithine was selected. That study found that the combination therapy reduced total metachronous colorectal adenomas by 70%, and advanced/multiple metachronous colorectal adenomas by more than 90% while also reducing colorectal polyamine levels.[41,50] No clinically significant toxicities were found to be statistically significant in that study. Clinically non-significant ototoxicities were identified in less than 10% of patients, using quantitative audiology methods.[34]

Recently, a clinical trial of eflornithine in combination with another NSAID for prevention of polyps in FAP patients has been reported. Lynch *et al*.[27,28] _ENREF_26have reported results of a trial using 500 mg/m^2/day eflornithine, rounded to the nearest 250 mg as 250 mg tablets were used in this study, combined with 400 mg BID celecoxib. After correcting for body surface area, the average eflornithine dosage was three (3) 250 mg eflornithine tablets PO daily. While the effect of the combination was not different from celecoxib alone for the primary endpoint (duodenal and colorectal polyp number), the Lynch *et al*. study provided evidence for effectiveness of the combination versus celecoxib alone (statistically significant reductions in the secondary endpoints of polyp volume and global polyp burden). No differences in toxicities, including ototoxicities, were observed between treatment arms in this study. Another study in non-FAP patients but relevant to potential safety issues of the higher eflornithine dose has also been reported. Bailey and colleagues treated 291 patients with prior non-melanoma skin cancers with 500 mg/m^2/day eflornithine for 4-5 years.[33] One patient was reported to have subclinical ototoxicity in that study. Long-term follow-up of these patients found no increase in adverse events in the treatment group compared to placebo.[33]

CPP FAP-310 will evaluate the eflornithine-sulindac combination in patients with FAP. These patients are at elevated risk for intestinal and colorectal polyposis and other events related to the fact that they harbor germline mutations in the adenomatous polyposis coli (APC) tumor suppressor gene. These genotypic FAP patients express higher levels of the eflornithine target gene, ornithine decarboxylase (ODC) and polyamine contents in apparently normal rectal mucosa than do non-genotypic familial controls.[44] These levels are higher than those reported for patients with sporadic risk of colorectal cancer.[51]

This study will use three (3) 250 mg eflornithine tablets daily in CPP FAP-310. This is based on both safety and efficacy considerations. Both the Lynch study (in FAP patients) and the Bailey study and others (in non-FAP patients) indicate safety of this eflornithine dose.[28,33] _ENREF_33 The Lynch study provides evidence for efficacy of the higher eflornithine dose in FAP patients.[28]

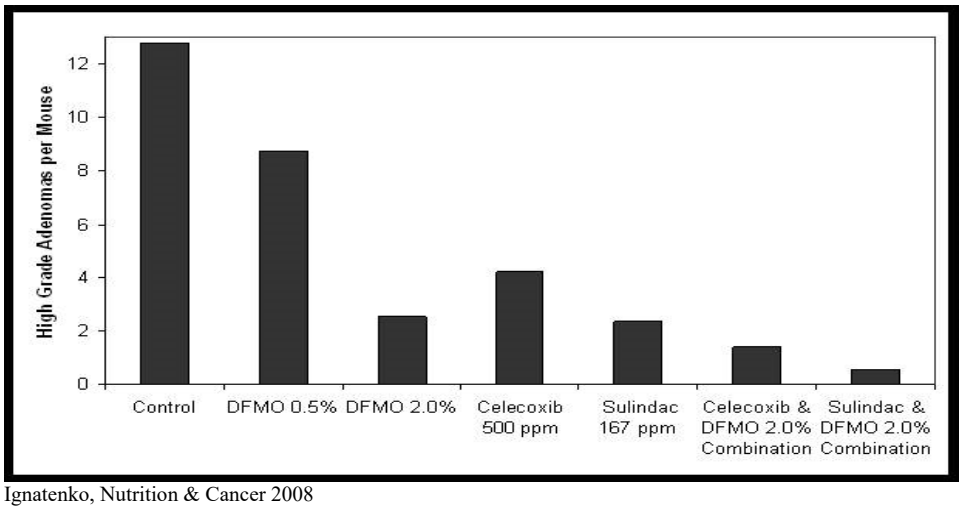
2.6. Rationale for Sulindac Dose

The dose of sulindac (daily oral dose of 150 mg) for this study was selected on knowledge of its physiology and evidence from preclinical and clinical studies.

Experimental findings in human cell and mouse models indicate that sulindac and other NSAIDS activate polyamine catabolism and export.[43] Thus, NSAID complement inhibitors of polyamine synthesis, like eflornithine, to reduce tissue polyamines. Cell culture data demonstrated that sulindac metabolites reduce cell survival in vitro in a dose dependent manner at doses above 150μM for 24 hour exposure times.[52]

Eflornithine-sulindac combinations are potent inhibitors of intestinal carcinogenesis in mouse models,[31] Figure 1.

Figure 1 - Eflornithine-Sulindac Combinations Mouse Model



Ignatenko, Nutrition & Cancer 2008

A detailed review of the clinical pharmacokinetic of sulindac has been written[53] and discusses long-term twice daily administration which results in accumulation of sulindac in the plasma, with the most common side effects being gastrointestinal and include pain, dyspepsia, nausea and gastrointestinal cramps.

Clinical studies demonstrate that a range of orally administered sulindac can cause regression of colorectal adenomas. In the review by Keller and Giardiello,[54] sulindac doses from 100 – 300 mg administered once or twice daily have been shown to cause regression of colorectal adenomas in patients with Familial Adenomatous Polyposis (FAP). Sulindac side effects noted in most of these studies were minimal although at the 300 mg/day of sulindac there may be an increase in cardiovascular risk in older high risk patients.

The studies summarized in the Keller and Giardiello review provides the clinical data to support the use of low doses of sulindac are effective in reducing colorectal adenoma burden in FAP patients[20,21,55,56,57,58] and that standard doses of sulindac (300-400 mg) are associated with significant toxicities. Therefore, a low dose of sulindac (150 mg) once per day was selected to be combined with eflornithine for treatment of patients with Familial Adenomatous Polyposis that are at high risk of developing rectal/intestinal cancer.

Sulindac used off label is often the choice of clinicians treating FAP patients today.[59] A commonly used sulindac dose in progressive rectal polyposis is 150 mg twice a day; after a few

months and demonstration of regression, dosage may be reduced to 150 – 200 mg daily (Burt, personal communication) or to 100 mg or lower.[55] There is no direct comparison between sulindac dosages. It is possible that the lower dose may be just as effective but requires a longer time to regression.

2.7. Summary of Known and Potential Risks

2.7.1. Cardiac Risk

A recent pooled-analysis of cardiovascular events in six clinical trials involving non-arthritis patients using celecoxib or placebo demonstrates that celecoxib is indeed associated with a dose-dependent increased risk of cardiovascular events[60] – high dose, long duration. In this analysis, three baseline cardiovascular risk categories were proposed: low, moderate, and high, using clinical information obtained from routine medical assessment. It was not known if these baseline cardiovascular risk assessments were associated with adverse cardiovascular events observed in the Phase III adenoma prevention trial of eflornithine plus sulindac (16 cardiovascular events occurred in this arm) compared with placebo (9 cardiovascular events occurred in the placebo arm). Therefore, members of the UC-Irvine group[61] performed detailed toxicity analysis of data from the Phase III eflornithine and sulindac versus placebo colorectal adenoma prevention trial, with a particular focus on baseline cardiovascular risk assessment. Cardiovascular toxicity outcomes were then reported with and without exclusion of high-risk patients from the analysis.

In the original sample of 184 placebo and 191 eflornithine/sulindac patients, respectively, baseline cardiovascular risk scores were evenly distributed (low: 27% vs. 30%, moderate: 34% vs. 29%, high: 39% vs. 41%). A greater number of patients with high cardiovascular risk at baseline experienced events in the eflornithine/sulindac arm (n=9) compared to placebo (n=3). When all patients with high baseline cardiovascular risk were excluded from the analysis, the number of cardiovascular events between the treatment (n=7) and placebo (n=6) arm was similar.[61] These results suggest a possible interaction between eflornithine/sulindac treatment and baseline cardiovascular risk score on cardiovascular events.

2.7.2. Ototoxicity Risk

In the Meyskens eflornithine/sulindac Phase III randomized placebo-controlled colon adenoma prevention trial[41], no significant differences in hearing loss were noted compared to placebo; however, minor differences in hearing loss attributed to eflornithine plus sulindac combination were observed in detailed longitudinal analyses.[34]

Temporary hearing loss is a known toxicity of treatment with eflornithine, thus a comprehensive approach was developed to analyze serial air conduction audiograms. The generalized estimating equation method estimated the mean difference between treatment arms with regard to change in air conduction pure tone thresholds while accounting for within-subject correlation due to repeated measurements at frequencies. Based on 290 subjects, there was an average difference of 0.50 dB between subjects treated with eflornithine plus sulindac compared with those treated with placebo (95% confidence interval, −0.64 to 1.63 dB; P = 0.39), adjusted for baseline values, age, and frequencies. In the normal speech range of 500 to 3,000 Hz, an estimated difference of 0.99 dB (−0.17 to 2.14 dB; P = 0.09) was detected. Dose intensity did not add information to models. There were 14 of 151 (9.3%) in the sulindac/eflornithine group and 4 of 139 (2.9%) in the placebo group who experienced at least 15 dB hearing reduction from baseline in 2 or more consecutive frequencies across the entire range tested (P = 0.02). Follow-up air conduction done at least 6 months after end of treatment showed an adjusted mean difference in hearing thresholds of 1.08 dB (−0.81 to 2.96 dB; P = 0.26) between treatment arms. There was no significant difference in the proportion of subjects in the sulindac plus eflornithine group who experienced clinically significant hearing loss compared with the placebo group. The estimated attributable risk of

ototoxicity from exposure to the drug is 8.4% (95% confidence interval, −2.0% to 18.8%; P = 0.12). However, there is only a <2 dB difference in mean threshold for patients treated with combination compared with those treated elsewhere (other trials) with placebo.

The eflornithine dose used in the Meyskens 2008 trial of patients with sporadic risk of colorectal cancer was 500 mgs orally per day for three years in combination with 150 mg daily sulindac.[41] No difference in ototoxicity was observed between NSAID alone and combination eflornithine NSAID arms in the Lynch trial of FAP patients, using an eflornithine dose of 750 mgs oral daily.[27,28] Bailey and colleagues have recently updated their study of patients with prior non-melanoma skin cancer that were treated with 500 mg/m^2 (also rounded to the nearest 250 mg as they used eflornithine tablets) for 4-5 years.[62] The Bailey study demonstrated a significant (P < 0.05) increase in uniformly transient audiometric (but not clinically detectable) hearing loss in participants on eflornithine.[33] The follow-up study did not report any clinically significant differences in hearing as compared to the placebo group.[62]

2.7.3. Sulindac Black Box Warning

Sulindac like other NSAIDS carries a black box warning to consumers that it may cause increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke which can be fatal and an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach and intestines which can be fatal. Refer to the Sulindac product insert (Actavis, formerly Watson Laboratories, Inc.)[63] and the recent FDA Drug Safety Communication[64] for further details. The sulindac dose in this trial is one-half the recommended anti-inflammatory dose.

3. TRIAL OBJECTIVES AND PURPOSE

3.1. Rationale

FAP is an orphan disease with multiple major unmet medical needs. The current standard of practice involves prophylactic colectomy or proctocolectomy, followed by proctoscopic intervention with surgical polypectomies and/or laser/cautery ablation every 6 – 12 months for the rest of their lives. Many patients have extensive polyposis at a young age and require surgery prior to entering college. Following prophylactic colon surgery, follow-up intervention by proctoscopy and upper GI endoscopy occurs every 6 – 12 months and subsequent surgical interventions are generally performed at experienced centers of excellence, requiring frequent, inconvenient and expensive travel. The serial interventions are unpleasant, require dietary restriction and enemas. During surgical procedures, some patients require general anesthesia and all patients require sedation. Surgical procedures for large or multiple adenomas may involve snare cautery polypectomy or trans-anal excision and carry risk of bowel perforation and or subsequent bleeding. The greater the frequency and extent of the surgical procedures, the greater the morbidity and associated costs. Such interventions frequently result in reduced compliance with medical and surgical recommendations, with subsequent increased likelihood of the development of an interval cancer. In addition, repeated cautery ablations lead to scarring and impaired bowel function over the years.

A major goal of this program is to defer or obviate the need for additional surgical interventions in patients with familial adenomatous polyposis. In patients treated with total abdominal colectomy with ileo-rectal anastomoses, the addition of sulindac combined with eflornithine has the potential to defer or eliminate the need for a complete proctectomy by polyp control which may result in less frequent and less extensive endoscopic or surgical interventions.

Prophylactic proctocolectomy does not “cure” patients with this genetic syndrome. FAP related disease remains a major problem in the residual rectum, pouch, anal transition zone, duodenum

and desmoid formation; both can lead to major morbidity and mortality. Surgical intervention is marginally effective, and there are no approved pharmacotherapeutic agents.

Fifty percent (50%) of patients following total proctocolectomy with ileal pouch anal reconstruction develop adenomas in the pouch and require the same extensive follow-up evaluations and surgical treatments. Almost all FAP patients are at risk for progressive duodenal adenomatous polyposis which can lead to extensive and frequent surgical endoscopic procedures and/or major surgical resections. Duodenal polyposis is a major cause of morbidity, mortality, patient inconvenience and health care costs in FAP patients. Ninety percent (90%) of patients with FAP develop duodenal polyposis[2] for which there is no approved pharmacologic agent to control this disease. Five (5) to 10% of patients have Spigelman Stage 4 on screening endoscopy; one-third of these patients develop cancer. Of greater concern from the Bulow analysis is that 52% of patients with duodenal polyposis who start with Stage 1, 2 or 3 will progress to Stage 4; the standard of care for Stage 4 is to consider some type of radical surgical intervention. The complexity of managing such patients is well described in the definitive review of FAP management guidelines by Vasen and colleagues.[10] The marginal benefit of endoscopic management of the duodenum is reviewed and tabulated (Table 4) in the paper by Brosens and colleagues.[65] The data clearly demonstrate the need and potential efficacy of the pharmacologic control of duodenal polyposis; using the well-established Spigelman staging system as an objective indicator of polyp burden, along with pre-malignant histology. The main determinant of Stage 4 is the presence of villous adenoma or high grade dysplasia on staging biopsies – objective measures of pre-cancerous risk.

Increasing the time to clinically meaningful endpoints relevant to standard of care by increasing the time to important FAP-related events (FAP-related surgery, duodenal polyposis, cancer and death) are key factors in regard to the morbidity and mortality of this genetic disease. FAP related surgical or clinical events in the rectum or pouch include surgery related to large or high risk adenomas or cancer; for FAP disease in the duodenum it includes surgery for enlarging or high risk adenomas.

After IRA surgery, pharmacologic control may minimize the need for additional rectal surgery (surgical snare excisions of polyps greater than 5 mm; surgical trans-anal excision of rectal polyps; proctectomy) and/or minimize development of pre-cancerous adenoma (dysplastic polyps, villous adenoma) and cancer. After pouch surgery it may minimize need for additional surgery (surgical snare excision of polyps greater than 5 mm, surgical trans-anal excision of rectal polyps, pouch resection with ileostomy) and/or minimize development of pre-cancerous adenomas and cancer.

In FAP patients with duodenal polyposis, pharmacologic control may suppress development of further polyposis, slow or prevent progression to Spigelman Stage 3 and 4 disease, minimize progression to dysplastic polyps or villous adenomas, minimize polyposis involving the Ampulla of Vater, minimize development of cancer or reduce the need for procedures such as snare polypectomy, submucosal excisions, trans-duodenal excisions, duodenectomy, Whipple (pancreatic duodenectomy) or related procedures.

Pharmacologic control in FAP patients has major implications for clinical benefit to reduce the morbidity of the disease and thereby improve the current standard of care. The use of low dose sulindac and CPP-1X may prolong the time to occurrence of clinically important FAP-related disease events (FAP related events include surgical procedures and progressive advanced intestinal polyposis).

In addition to the above, the combination drug regimen may provide additional clinical benefit by,

- Deferring the initial prophylactic colectomy to a more "convenient time" such as after graduation from school or after childbirth.
- Increasing the use of colectomy with ileal-rectal reconstruction rather than total proctocolectomy which results in improved quality of life in regard to bowel function and reduces the risk of loss of fertility in women.
- Reducing the risk of progressive rectal/pouch polyposis that requires surgical intervention.
- Reducing the risk of rectal stump/pouch-related post polypectomy scarring with loss of bowel function (absence of compliant rectal reservoir).
- Deferring or obviate the need for pouch removal with need for permanent ileostomy stoma.
- Deferring or obviate the need for surgical intervention for advanced duodenal polyposis with associated morbidity and mortality.
- Improving health-related quality of life (HRQoL).

3.2. Rationale for Treatment Duration Extension up to 48 Months

The initial statistical analysis plan used detailed event rate projections based on an extensive review of the published literature (Refer to Appendix E) and determined that a sample size of 150 randomized subjects would be required for the primary endpoint analysis. Because of logistical reasons, subject accrual was completed in April 2016 with 171 patients randomized.

In February 2016, a blinded data review was done to project a more realistic estimate of FAP-related event rates at the completion of the trial with a maximum of 24 months of treatment. Based on this analysis, it was considered unlikely we would reach the projected 90 events before the end of the study. To reduce the risk of a false-negative trial (because of inadequate events after two years of study treatment in 171 randomized subjects), several mitigation options were explored. The protocol was amended to extend treatment duration to a maximum of 36 months. Over 90% of subjects who reached 24 months without an FAP-related event consented to the trial extension.

As of June 2017, there have been 53 FAP-related primary endpoint events. Under the current event rates and with an estimated trial end-date of April 2018, projections once again do not indicate a high likelihood of 90 events. Various statistical analyses, using Weibull methodology, indicate that under current hazard rate assumptions to maintain power $\geq$ 85%, an additional trial extension may be required. This protocol amendment offers all active subjects a longer-term blinded treatment until study completion at or before April 2019. This means, based on the date of randomization, a treatment extension of up to 36, 42 or 48 months. The study will complete for reasons defined in Section 4.2.

There have been five safety data monitoring committee meetings for CPP FAP-310 study**,** the most recent June 2017. To date, the DMC has not identified any safety issues and there have been no recommended protocol modifications due to safety. Additionally, for CPP FAP-310, the Medical Monitor performs a monthly blinded review of all adverse events to evaluate for events not commonly associated with drug exposure or to look for an increase in events above what is typical for the population under study.

At the time of the amendment for the treatment extension, there have been twenty-six (26) serious adverse events (SAEs) that have been reported from the CPP FAP-310. Two events were classified as SUSARs; however, no subject treatment arm assignments were unblinded.

Twenty-one (21) of the twenty-six (26) SAEs were classified as not related to study treatment by the study investigators. There were eleven (11) gastrointestinal events. These included five (5) small bowel/intestinal obstructions. This type of event is not uncommon in the FAP population, particularly those with multiple surgeries. There was one (1) gastrointestinal events of ileus and one (1) ileal stricture. The subject with ileus had additional episodes prior to taking the study drugs. Ileus and ileal stricture are expected events in the FAP and post colon surgery patient populations. There was also one (1) event of rectal bleeding that was from a post-polypectomy ulceration. Bleeding is a common complication from an endoscopic excision and there was also one (1) procedural complication that involved a post-polypectomy bleed.

There was one (1) event of pancreatitis in a subject with a prior history of pancreatitis and one (1) subject with acute pancreatitis. The subject with pancreatitis was hospitalized for six weeks and the event was a life-threatening, grade 4 serious adverse event. In the case of acute pancreatitis, the investigator indicated that the likely cause was ampullary adenomatous disease. FAP patients are at a higher risk of pancreatitis than the general population[66]**.** Pancreatitis is a rare, but identified risk of sulindac. The Investigator's Brochure, Sulindac package Insert and published reports indicate that pancreatitis is associated with the use of sulindac.[67]

One (1) subject experienced grade 3 constipation which quickly resolved with evacuation and pain management. Although constipation is a common side effect of both eflornithine and sulindac as documented in the Investigator's Brochure, the investigator evaluated as not related due to the timing and rapid resolution of the event.

There was one (1) event in the nervous system disorders category that was a seasonal migraine in a subject had a history of this type of event. For neoplasms, there was one (1) diagnosis of lung adenocarcinoma with a brain lesion, unrelated to treatment. There was also one (1) event of chronic myeloid leukemia, unrelated to treatment. In addition to the post-polypectomy bleed described above, there were three other (3) events in the injury/complications category. There was one (1) wound complication related to cellulitis of an incarcerated umbilical surgical scar. This was unrelated to study treatment and related to multiple prior surgeries. One (1) event of seroma complication post-desmoid surgery was unrelated to treatment and is a known complication of abdominal surgery. The one (1) event of anastomotic stricture was a hospitalization for the treatment of a pre-existing anal stenosis and was unrelated to treatment. One subject had perforated knee bursitis, likely infectious in origin, that was classified as unrelated to study medication. One (1) subject with pre-existing COPD experienced an exacerbation that required medication and oxygen therapy, but was not related to treatment. The subject with acute pancreatitis described above also experienced grade 3 hyperglycemia and was diagnosed with type 2 diabetes. This event was unlikely to be related to treatment, but is reported to be a very rare complication of sulindac and is listed in the Investigator's Brochure.

The remaining five (5) events were classified as being possibly (4) or probably (1) related to treatment. One (1) event of worsening of depression was listed as possibly related to treatment. Depression is covered in the Reference Safety Information as a known side effect of sulindac and with the side effect of emotional lability for eflornithine. For vascular disorders, there was one (1) thromboembolic event (DVT without pulmonary embolism) listed as possibly related to treatment. This is a known risk of sulindac and is listed in the Reference Safety Information in the Investigator's Brochure. One (1) subject experienced severe nausea (grade 3) approximately

4 months after study treatment began. This was possibly related to treatment; nausea is listed as a complication of both eflornithine and sulindac.

There were two (2) events that were classified as SUSARS. One (1) subject experience psychosis and paranoia, grade 3. This began 6-8 weeks prior to the month 24 end of treatment visit and progressed to the point of paranoid psychosis resulting in hospitalization and treatment with anti-psychotic, anxiolytic and insomnia medications. The investigator assessed this event as possibly related. Eflornithine has a known side effect of emotional lability and sulindac has an uncommon side effect of psychic disturbances, including acute psychosis, both listed in the Reference Safety Information. After discharge, the subject completed the study. The second SUSAR was a spontaneous abortion. The subject had a positive pregnancy test and stopped study medication upon confirmation. Approximately 2 months after discontinuation, the subject lost the fetus due to a suspected placental abruption. The subject had a history of miscarriage and the event was classified as possibly related. The Sponsor determined that the SAE of spontaneous abortion was not related to the study medication. Eflornithine is known to be embryotoxic in animal studies and is listed as a safety risk in the Investigator's Brochure.

The constituents for this combination therapy, eflornithine and sulindac, are considered as having well-established medicinal use within the meaning of Annex I to Directive 2001/83. Both active substances have been authorized in medicinal products for various therapeutic indications for doses, duration and frequency exceeding that which is used in the CPP FAP-310 Phase III clinical study. Randomized clinical trials of eflornithine and sulindac alone or in combination indicate that these agents have minimal toxicities when used for treatment periods of 3 or more years in patients with risk of cancer. The minimal toxicities observed to date in CPP FAP-310 for treatment of FAP patients with eflornithine and sulindac for up to 3 years supports the extension of the treatment time in CPP FAP-310 from 3 to up to 4 years at a dose level of 750 mg/day eflornithine and 150 mg/day sulindac.

This protocol amendment may extend the trial by up to 12 months, and offers subjects (based on their randomization date) treatment up to 48 months. The end of study will not be beyond April 30, 2019. Actual duration of treatment for each subject is based on the occurrence of an FAP-related event, censoring for standard reasons unrelated to FAP-related endpoint indicators, or the final end of study date. In the absence of an FAP-related event, subjects will receive study treatment for 24 to 48 months. The final decision concerning the trial end-date if prior to April 30, 2019, will be based on accrued FAP-related primary endpoints, number of subjects still active on trial, FAP event projections, and additional safety reviews. Assuming continued acceptable safety profile, this approach will minimize the risk of a false negative trial.

3.3. Purpose

This randomized, double-blind, phase III trial will compare the efficacy, safety and pharmacokinetics of the CPP-1X/sulindac combination versus CPP-1X and sulindac as single agents with up to a 48-month maximum treatment period in patients with Familial Adenomatous Polyposis (FAP).

4. INVESTIGATIONAL PLAN

4.1. Study Population

- Diagnosis of phenotypic classical FAP, age ≥18 years, male and female gender. Must be genotyped, with an APC mutation. Refer to Section 6.1 for details.
- Meets eligibility criteria for at least one FAP related disease group defined in Section 6.1.
- If prior colorectal surgery, at least three years since colectomy with ileal-rectal anastomosis (IRA) or total proctocolectomy with ileal pouch-anal reconstruction (pouch).
- Absence of major cardiac risk factors as defined in Section 6.2.
- Absence of clinically significant hearing loss requiring a hearing aid.
- Adequate laboratory studies (hematology, chemistry, and urinalysis) at study entry.

4.2. Treatment

- Experimental arm: 750 mg CPP-1X, and 150 mg sulindac
- Comparator arms:
    1. CPP-1X placebo with sulindac (150 mg)
    2. CPP-1X (750 mg) with sulindac placebo
- Treatment is administered as four tablets taken once daily with food (same time of day, preferably in the morning), for up to 48 months.
- Randomized subjects will receive 24 months of treatment and complete their final assessment or come off-study for an FAP-related event or for other reasons (for example, safety issues, non-compliance, withdrew consent, lost to follow-up).
- Subjects completing 24 months of treatment without an FAP-related event can continue on treatment for up to 48 months based on their randomization date as follows:

    1. If randomized between November 2015 and April 2016 eligible for up to 36 months of treatment
    2. If randomized between May 2015 and October 2015 eligible for up to 42 months of treatment
    3. If randomized between July 2014 and April 2015 eligible for up to 48 months of treatment

    or until one of the following occurs:

    1. Subject has an FAP-related event or comes off study for other reasons
    2. Trial end-date of April 30, 2019 has been reached
    3. 90 FAP-related events have occurred
    4. Less than 90 FAP-related events have accrued prior to April 30, 2019 and an earlier trial end-date has been set by the Sponsor and reviewed by the DMC
    5. An earlier trial end date prior to April 30, 2019 has been recommended by the DMC for safety reason and approved by the Sponsor

4.3. Randomization

At least 150 eligible patients will be enrolled in this study. Subjects will be randomized to one of three treatment groups in equal proportions (i.e., 1:1:1 randomization): 1) CPP-1X plus sulindac 2) CPP-1X - placebo plus sulindac, 3) CPP-1X plus sulindac placebo.

A stratified randomization procedure will be used with stratification based on FAP-related time-to-first-event prognosis. The event prognosis groups are represented by 1) best (i.e., longest projected time to first FAP-related event) - rectal/pouch polyposis, 2) intermediate - duodenal polyposis, and 3) worst - pre-colectomy. If a subject has two or more of these disease sites, the most severe prognosis stratum will be assigned for randomization (e.g. worst > intermediate > best). Since an individual may have more than one disease site involved, the trial will assess time to any defined FAP-related event in the subject as a whole. In order to minimize potential treatment arm imbalance a centralized randomization process will be used to balance among treatment groups within prognostic strata.

4.4. Primary Outcome

The primary objective of this trial is to determine whether the combination of CPP-1X plus sulindac is superior to either treatment individually, in delaying the time from the date of randomization to the date of the first occurrence of any FAP-related event in the subject as a whole. This includes: 1) FAP related excisional intervention involving the colon, rectum, pouch, duodenum and/or 2) clinically important events which includes progression to more advanced duodenal polyposis (Stage 2, 3 or 4), cancer or death. Section 8.2.14 provides complete detail.

4.5. Secondary Outcomes

Secondary Efficacy Analyses:

Any improvement observed by the investigator during upper gastrointestinal (UGI) and lower gastrointestinal (LGI) visualization (i.e. endoscopy and colonoscopy) at the 6 and 12-month study visits will be described using the variables UGI Observed Improvement (UGIOI), and LGI Observed Improvement (LGIOI). Each patient will have one pair of UGIOI and LGIOI outcomes (refer to Protocol Section 12.0 and the Statistical Analysis Plan for more detail).

Other Secondary Outcomes in this Study Include the Following:

To explore how study treatment group relates to other efficacy outcomes, genotype, phenotype, disease locations and endoscopic findings, additional analyses are planned (refer to the Statistical Analysis Plan for more details).

The UGIOI and LGIOI outcomes will be tabulated and summarized using the month 6 visit scores, alone. Similarly, the UGIOI and LGIOI outcomes will tabulated and summarized across all study visits.

As both part of the primary analysis, and further explored in these additional analyses, median time to event for each treatment group will be determined. This will be explored for each of the study populations (i.e. ITT, per protocol, and others), study disease stratum groups, and in the disease site subgroups.

Pharmacokinetic data (plasma concentrations measured at patient visits) will be used to estimate population pharmacokinetic parameters for the CPP-1X (eflornithine), sulindac, and CPP-1X (eflornithine) + sulindac treatment groups (i.e., for each analyte for those patients on combination treatment).

The subcategories of FAP events will be explored by disease stratum groups, and by disease site subgroups.

The presence or absence of ODC polymorphisms, including the single nucleotide polymorphisms (SNPS) rs2302615 and rs2302616 and their relation to treatment group and outcome will be tested with the likelihood ratio test.

The excretion of 5 urinary polyamines (diacetylspermine, n1-acetylspermidine, n8-acetylspermidine, decarboxylated SAM, and putrescine) will be assessed in relation to treatment group and outcome, using the single point concentration data gathered from the urine samples harvested at each study visit.

Patient reported health related quality of life measures will be evaluated using HRQoL.

Tissue and dietary polyamine levels, as collected at patient study visits will be analyzed together with the results of the dietary questionnaires and related to treatment group and study outcomes.

Safety outcome data and analyses are described in detail in the Statistical Analysis Plan.

4.6. Population Pharmacokinetics for CPP-1X/Sulindac

All subjects consented, enrolled, and randomized in this study will have pharmacokinetic samples drawn at their scheduled 3-month visit. All subjects will have samples drawn on the same schedule regardless of treatment arm assigned. The samples will be obtained before first morning dose, then four additional samples over the following eight hours.

4.7. Polyamine Analysis

At each colonoscopy/proctoscopy while on study treatment, a sample of normal rectal mucosa and a random urine sample will be obtained to assess tissue and urine polyamine levels. Sample handling and processing procedures will be provided in the study manual, are described here briefly.

Biospecimen collection: Normal (tumor-free) rectal mucosal biopsies will be obtained during endoscopy procedures. Biopsy samples will be placed in separate standard cryotube tubes and stored in a -70 – 80^0C freezer. Random urine samples (15 mL minimum) will be collected and stored in a -70 – 80^0C freezer.

Polyamine content: Polyamine analysis will be performed as described previously.[35] Briefly, frozen tissue samples will be homogenized and extracted in 0.2 N perchloric acid. Urine samples will be adjusted to 0.2 N perchloric acid. Polyamine (spermidine, spermine, and putrescine) content will be measured using reverse-phase, ion-paired high performance liquid chromatography. Protein contents will be determined using the bicinchoninic acid protein assay (Thermo Fisher Scientific, Rockford, IL). The spermidine-to-spermine ratio (Spd:Spm) will be assessed in our analyses to minimize the influence of assay variability.[35,68]

Dietary polyamines: Data will be collected using the Fred Hutchinson Cancer Center food frequency questionnaire and will be analyzed using a polyamine database. Average daily consumption of putrescine, spermidine, and spermine will be calculated.[69]

4.8. Pharmacogenetic and Genetic Analysis

A peripheral blood sample will be collected from enrolled subjects at baseline for subsequent correlative genomic studies relevant to this disease and in the event treatment-related adverse events are discovered during the trial. Sample handling and processing procedures, which will be provided in the study manual, are described here briefly.

DNA extraction and genotyping. DNA will be extracted from peripheral blood samples using the QIAGEN QIAamp DNA Midi or Mini Kits (Qiagen), following the manufacturer's instructions. Genotyping of the ODC1 (National Center for Biotechnology Information SNP database ID rs2302615) +316 SNP will be conducted using a PCR amplification of the targeted region and bi-directional cycle sequencing of purified target amplicon using PCR/Sanger sequencing primers. The sequencing reaction will be analysed on an Applied Biosystems 3730 Genetic Analyzer. The PCR amplicon will be sequenced in both forward and reverse directions to confirm the SNP.

4.9. Quality of Life

Assessment of Health-Related Quality of Life (HRQoL) is to better understand and quantify the impact of each treatment arm on FAP-related physical and emotional symptoms as well as FAP-related surgical sequelae. Specifically, postponing surgery because of reduction of polyps could lead to both symptomatic relief as well as reduced stress and worry about cancer, future surgery and/or suffering of FAP-related medical and surgical symptoms. As such, several well-accepted and previously published questionnaires have been selected for use in the CPP FAP-310 trial. These include the EORTC core questionnaire, QLQ-C30,[70] the GI-specific sub-module, QLQ-CR29,[71] and the EQ-5D health utilities index.[72,73] These instruments have all been previously used in gastrointestinal/colorectal clinical trials and have been validated and translated to ensure appropriate cultural/linguistic adaptation suitable for a multi-center, international clinical trial. Also being used is a modified version of the Cancer Worry Scale.[74]

5. STUDY DRUG INFORMATION

5.1. CPP-1X [Eflornithine HCl]

Eflornithine, also known as DFMO, is an inhibitor of ornithine decarboxylase (ODC) designated chemically as 2-(difluoromethyl)-DL-ornithine.

The clinical dosage form of CPP-1X (eflornithine HCl) is a yellow, film-coated convex tablet containing 231 mg per tablet of anhydrous eflornithine HCl as eflornithine HCl monohydrate (250 mg per tablet).

[redacted]

The tablets are to be stored at room temperature (20-25^{0}C).

Study subjects will be instructed to take three (3) tablets by mouth once daily with food.

[redacted]

5.1.1. Eflornithine Clinical Pharmacology

Eflornithine hydrochloride is a member of the following drug classes: 1) inhibitor of ornithine decarboxylase (ODC), 2) hirsutism (excess hair growth) retardant, and 3) antiprotozoals. Eflornithine is FDA approved as a cream for treatment of female hirsutism, and in intravenous form for treatment of trypanosomiasis. The oral tablet form is not available outside of the clinical trial setting in the US and EU. [redacted]

Contraindications: Prior hypersensitivity to eflornithine. Precaution in patients with bone marrow suppression or hematologic disorders.

Common side effects: Low platelet count was dose-limiting after administration of intravenous eflornithine at high doses (up to 3 gm/m^2 every 6 hours for 28 days). Gastrointestinal upset (nausea, vomiting [5%], diarrhea [38%]) have also been reported after these high doses of eflornithine. The primary side effect of low doses of eflornithine (750 mg per day for 3-5 years) is mild ototoxicity with 45.2% of eflornithine subjects versus 33.6% of placebo subjects having a

≥15 dB hearing loss at two adjacent frequencies (p=0.07). The observed audiometric abnormalities were usually reversible; 19% and 18% of eflornithine and placebo subjects had persistent abnormal audiograms 6 months after stopping study drug.[33]

Infrequent side effects: Hearing loss/change by audiometry testing has been reported in 8.4% of patients on high dose eflornithine. Rash and alopecia have been reported in 3% of patients. Anorexia and abdominal pain have been reported in 2% of patients treated with eflornithine.

Rare but serious side effects include dizziness (1%), headaches (2%), and seizures (8%) have been reported in patients on intravenous eflornithine. Myelosuppression (including leukopenia, [37%], anemia [55%], and thrombocytopenia [14%]) has been reported at high intravenous doses, but does not usually occur at the low dose (750 mg) utilized in this study.[33]

Pregnancy and Lactation: Pregnancy Category C. It is unknown if eflornithine crosses the placenta. Case reports in humans along with animal studies (mice, rats) indicate potential for fetotoxicity. Experiments in rodents indicate that eflornithine blocks yolk sac formation and trophoblast differentiation, affecting processes such as vasculogenesis and steroidgenesis.[75] The World Health Organization has not determined a breast-feeding rating for eflornithine due to insufficient data. The Thompson lactation rating is that infant risk cannot be ruled out. No studies investigating the safety of lactation after eflornithine administration have been conducted, nor are there data to determine drug levels in breast milk after drug administration.

5.1.2. CPP-1X (Eflornithine) Pharmacokinetics

The dose of CPP-1X (daily oral dose of 750 mg for an adult) for CPP-310 was selected based upon its known pharmacology and evidence from clinical studies.

Time to peak concentration for oral eflornithine is 4-6 hours.

Absorption: for the oral solution is 54-58% and is unaffected by feeding status.

Distribution: no protein binding sites, crosses blood-brain barrier, volume of distribution is 0.3-0.35 liters/kg.

Metabolism: urinary recovery of unchanged drug as eflornithine is 86% and essentially not metabolized.

Excretion: renal excretion. Elimination half-life: 3-3.5 hours but once daily oral dosing of 500-750 mg is sufficient to maintain efficacy as indicated in several clinical trials.

Eflornithine pharmacokinetic references include, Abeloff, *et al.,* 1984,[76] Haegele *et al.,* 1981,[77] Meyskens, *et al.*, 1998,[35] and Meyskens *et al*., 2008.[41]

5.2. Sulindac

Sulindac is a non-steroidal, anti-inflammatory indene derivative designated chemically as (Z)-5-fluoro-2-methyl-1- [[*p*- (methylsulfinyl)phenyl]methylene]-1*H*-indene-3-acetic acid. It is not a salicylate, pyrazolone or propionic acid derivative. Sulindac, a yellow crystalline compound, is a weak organic acid practically insoluble in water below pH 4.5, but very soluble as the sodium salt or in buffers of pH 6 or higher. [redacted] Sulindac tablets (USP) 150 mg tablets are round yellow tablets imprinted DAN and 5661 and are supplied in bottles of 100. Dispense in a well-closed container with child-resistant closure. [redacted]

Sulindac is marketed in the US for relief of signs and symptoms of the following conditions: osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute painful shoulder (bursitis/tendinitis), and acute gouty arthritis.

The sulindac tablets are to be stored at room temperature (20-25^{0}C).

Study subjects will be instructed to take one (1) tablet by mouth daily with food.

5.2.1. Sulindac Clinical Pharmacology

Sulindac is a nonsteroidal anti-inflammatory analgesic that inhibits both cyclooxygenase COX I and COX II.

Contraindications: Treatment of post-operative pain after coronary artery bypass grafting (risk of stroke, myocardial infarction). Hypersensitivity to sulindac or excipient byproducts. Hypersensitivity to aspirin or other NSAIDs.

Common side effects: As with other NSAIDs, sulindac can produce gastric pain (10%), constipation (3-9%), diarrhea (3-9%), dyspepsia (3-9%), and nausea (3-9%). Dizziness (3-9%), headache (3-9%), and rash (3-9%) have also been reported. Additionally, this side effect is seen most often in patients who have had prior ulcers or who are taking anticoagulants or steroids or who have abnormal renal or liver functions; potential patients who have these parameters will not be eligible for study entry. At therapeutic doses, gastrointestinal pain occurs in 10%.

Infrequent side effects: Flatulence, cramping, anorexia, vomiting, pruritus, nervousness, tinnitus, and edema (1-3%) have been reported. Gastrointestinal ulcers have been reported in 2-4% of patients taking NSAIDs. Bleeding may occur due to platelet inhibition. Gastrointestinal ulceration in general is dose-related (the dose used in the current trial will be 50% that typically used). Its potential interaction with eflornithine effect (i.e., possibly delay in wound healing) is unknown.

Rare but serious side effects ($\geq$ 1%): Hypertension, arrhythmias, thrombotic events, Stevens-Johnson syndrome and Toxic Epidermal Necrolysis (TEN) have been reported for various NSAIDs at low frequency. Hyperkalemia, esophagitis, gastrointestinal hemorrhage, gastrointestinal perforation, and pancreatitis have been reported for NSAIDs including sulindac. Anemia, agranulocytosis, leucopenia, thrombocytopenia, aplastic anemia (rare), nephrotoxicity, hyperthermia, pneumonitis, bronchospasm, and hepatotoxicity have been reported after sulindac use. Blurred vision, alopecia, anaphylaxis, bitter taste, aseptic meningitis, bone marrow suppression, and seizures have been reported.

Pregnancy and Lactation: Pregnancy Category C. Sulindac crosses the placenta. There have been no reports of congenital abnormalities caused by maternal use of sulindac. However, sulindac should be avoided in late pregnancy because of the effects of prostaglandin inhibition (closure of the ductus arteriousus) on the fetal cardiovascular system. It is not known whether this drug is excreted in human milk; however, it is secreted in the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from sulindac, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. Refer to the Sulindac product insert (Actavis, formerly Watson Laboratories, Inc.)[78] for additional information.

5.2.2. Sulindac Pharmacokinetics

Refer to the Sulindac product insert (Actavis, formerly Watson Laboratories, Inc.)[78] for additional information.

Absorption: 90% bioavailability; sulindac must be metabolized to the sulfide metabolite before it is pharmacologically active.

Distribution: Sulindac and its sulfone and sulfide metabolites are 93.1, 95.4 and 97.9% bound to plasma proteins. Sulindac penetrates the blood-brain barrier and placental barriers.

Metabolism: Sulindac and its sulfone metabolite undergo extensive enterohepatic circulation relative to the sulfide metabolite in animals.

Kinetics: T_{max} for sulindac (150 mg tablet) is 3.9 ± 2.3 hours, and 5.85±4.5 hours for the sulfone metabolite and 6.2 ± 3.1 hours for the sulfide metabolite.

Elimination: Approximately 50% of the administered dose of sulindac is excreted in the urine with the conjugated sulfone metabolite accounting for the major portion. Less than 1% of the administered dose of sulindac appears in the urine as the sulfide metabolite. Approximately 25% is found in the feces, primarily as the sulfone and sulfide metabolites. The mean effective half-life ($T_{1/2}$) for sulindac is 7.8 hours and 16.4 hours for the active sulfide metabolite.

6. SUBJECT RECRUITMENT, INCLUSION AND EXCLUSION CRITERIA

Subjects (male and female), ≥ 18 years will be recruited who meet the inclusion criteria below. Women and minorities will be represented according to their distribution in the Investigator's clinical population.

6.1. Patient Characteristics for Eligibility, Inclusion Criteria

1. Diagnosis of phenotypic classical FAP with disease involvement of the duodenum and/or colon/rectum/pouch.
    a) Genotype: APC mutation (with or without family history) required
    b) Classical FAP Phenotype: 100's to 1,000's of colorectal adenomatous polyps, usually appearing in teenage years
2. UGI endoscopy/LGI endoscopy (proctoscopy/colonoscopy) performed within 30 days of randomization.
3. Patients with an intact colon/rectum and prophylactic surgery is being considered as a stratification site.
4. Rectal/pouch polyposis as a stratification site as follows:

    4.a At least three years since colectomy with IRA/proctocolectomy with pouch, and demonstrating polyposis as defined by Stage 1, 2, 3, of the proposed InSiGHT 2011 Staging System (Appendix B) and summarized as follows:

    Stage 1: 10-25 polyps, all < 5 mm

    Stage 2: 10-25 polyps, at least one > 1 cm

    Stage 3: >25 polyps amenable to complete removal, or any incompletely removed sessile polyp, or any prior evidence of high grade dysplasia, even if completely removed. [Note: For staging purposes only.]

    4.b **For all subjects, any rectal/pouch polyps > 5 mm must be excised at "baseline".**

5. Duodenal polyposis as a stratification site; one or more of the following:

    5.a Current Spigelman Stage 3 or 4. (Refer to Appendix A for Modified Spigelman Score and Classification table).

    5.b Prior surgical endoscopic intervention within the past six months for Spigelman Stage 3 or 4 that may have been down staged to Spigelman 1 or 2.

6. Hematopoietic Status (within 30 days prior to randomization):
    a) No significant hematologic abnormalities
    b) WBC at least 3,000/mm^3
    c) Platelet count at least 100,000/mm^3
    d) Hemoglobin at least 10.0 g/dL
    e) No history of clinical coagulopathy

7. Hepatic Status (within 30 days prior to randomization):
    a) Bilirubin no greater than 1.5 times ULN
    b) AST and ALT no greater than 1.5 times ULN
    c) Alkaline phosphatase no greater than 1.5 times ULN
8. Renal Status (within 30 days prior to randomization):
    a) Creatinine no greater than 1.5 times ULN
9. Hearing:
    a) No clinically significant hearing loss, defined in Section 6.2, number 9.
10. If female, neither pregnant nor lactating.
11. Negative pregnancy test if female of child-bearing potential. Fertile patients must use effective contraception*. Confirmation of postmenopausal status unless surgically sterile**.
12. Absence of gross blood in stool; red blood on toilet paper only acceptable.
13. No discrete gastric or duodenal ulcer greater than 5 mm within the past year except Helicobacter pylori-related peptic ulcer disease treated with antibiotics.
14. No invasive malignancy within the past 5 years except resected non-melanomatous skin cancer, papillary thyroid cancer, or precancerous cervical dysplasia.
15. No other significant medical or psychiatric problems that would preclude study participation or interfere with capacity to give informed consent.
16. Use of 81 to 100 mg daily aspirin or up to 700 mg aspirin not more than once a week are eligible.
17. No concurrent warfarin, fluconazole, lithium, Pradaxa® or other direct thrombin inhibitors, Plavix®, cyclosporine, other NSAIDs (such as ibuprofen, aspirin in excess of 700 mg weekly, diflunisal), diuretics (furosemide and thiazides), DMSO, methotrexate, probenecid, propoxyphene hydrochloride, Tylenol® (acetaminophen) preparations containing aspirin or cytotoxic chemotherapy drugs.
18. Willingness to forego concurrent use of supplements containing omega-3 fatty acids, oral corticosteroids, non-steroidal anti-inflammatory drugs or other FAP directed drug therapy.
19. Able to provide written informed consent and follow protocol requirements.

*Fertile male or female, effective contraception methods include the established use of oral, injected or implanted hormonal methods of contraception, placement of an intrauterine device (IUD) or intrauterine system (IUS), barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate), or true abstinence, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Contraceptives should be used during the study and for at least 2 weeks after study treatment.

Male subjects (including men who have had vasectomies) whose partners are pregnant should use condoms while the partner is pregnant. If the partner is still pregnant when the subject goes off study, the subject should continue condom uses for at least 2 weeks afterwards.

**Postmenopausal status may be confirmed by any of the following: a) ≥ 12 months spontaneous amenorrhea; b) 6 months spontaneous amenorrhea with serum FSA levels > 30 IU/L[79,80]; c) ≥ 6 weeks postsurgical bilateral oophorectomy; d) ≥ 6 weeks postsurgical hysterectomy.

6.2. Exclusion Criteria

1. Prior pelvic irradiation.
2. Patients receiving oral corticosteroids within 30 days of enrollment.
3. Treatment with other investigational agents in the prior 4 weeks.
4. Use of other non-steroidal anti-inflammatory drugs (such as ibuprofen) exceeding 4 days per month, in the prior 6 weeks.
5. Regular use of aspirin in excess of 700 mg per week.
6. Treatment with other FAP directed drug therapy (including sulindac or celecoxib, fish oil) within 12 weeks of study enrollment.
7. Hypersensitivity to cyclooxygenase-2 inhibitors, sulfonamides, NSAIDs, or salicylates; NSAID associated symptoms of gastritis.
8. Patients must not have cardiovascular disease risk factors as defined below.
   - Uncontrolled high blood pressure (systolic blood pressure > 150 mm Hg;
   - Unstable angina;
   - History of documented myocardial infarction or cerebrovascular accident;
   - New York Heart Association Class III or IV heart failure (Refer to Appendix C);
   - Known uncontrolled hyperlipidemia defined as LDL-C ≥ 190 mg/dL or triglycerides ≥ 500 mg/dL.
9. Patients with significant hearing loss are not eligible for study participation as defined below.
   - Hearing loss that affects everyday life and/or for which a hearing aid is required.
10. Intact colon/rectum or retained rectum or ileal pouch:
    a) cancer on biopsy
    b) high grade dysplasia found on polyp biopsy where the polyp is not completely removed
    c) a large polyp (>1 cm) not completely removed.
11. Duodenal cancer on biopsy.
12. Intra-abdominal desmoid disease, stage III or IV (staging criteria in Appendix D).[9,81]
13. Inability to provide informed consent.

6.3. Replacements and Screen Failures

Randomized subjects who discontinue early for any reason will NOT be replaced and will not be permitted to reenter the study.

Previously screened subjects may be rescreened for enrollment in the study with prior approval from the Medical Monitor. Subjects who are rescreened 30 days after signing the informed consent will need to be re-consented and have all screening procedures repeated to determined eligibility.

Any screen failed subject based on history, physical exam or laboratory values or endoscopy procedures will need to have a screen failure case report form completed by the Investigator or study coordinator and available for review by the study Sponsor.

7. RANDOMIZATION AND STRATIFICATION

Subjects eligible for this trial will be randomized into one of three treatment groups 1:1:1 (CPP-1X plus sulindac: CPP-1X placebo plus sulindac: CPP-1X plus sulindac placebo) and stratified by FAP-related event prognosis using an interactive web-based system as described below. Subjects will be randomized no more than 5 working days prior to their scheduled start date of treatment.

A stratified randomization procedure will be used with stratification based on FAP-related time-to-first-event prognosis. The event prognosis groups are represented by 1) best (i.e., longest projected time to first FAP-related event) - rectal/pouch polyposis, 2) intermediate - duodenal polyposis and 3) worst - pre-colectomy. If a subject has two or more of these disease sites, the most severe prognosis stratum will be assigned for randomization (e.g. worst > intermediate > best). Since an individual may have more than one disease site involved, the trial will assess the time from the date of randomization to the date of the first occurrence of any FAP-related event in the subject as a whole. In order to minimize potential treatment arm imbalance a centralized randomization process will be used to balance among treatment groups within prognostic strata.

8. SPECIFIC TREATMENT PLAN AND SUBJECT MANAGEMENT

8.1. Subject Assessments and Treatment Schedule

The clinical study schedule/schema (Table 3) provides the schedule for screening, on-study visits and follow-up.

Table 3 - FAP Study Schedule (Initial 24 Months of Treatment)

	Screening /Baseline	Mo. 0-1-2	Mo. 3	Mo. 4-5	Mo. 6	Mo. 7 -8	Mo. 9	Mo. 10-11	Mo. 12	Mo. 13-14	Mo. 15	Mo. 16-17	Mo. 18	Mo. 19-20	Mo. 21	Mo. 22-23	24 mo. /EOT	FU 30 days Off-Study	FU Mo. 2-6 Off Study
Procedures		(± 1 wk)			(± 2 wks)	(± 1 wk)			(± 2 wks)	(± 1 wk)			(± 2 wks)	(± 1 wk)			± 2 wks[21]	(± 1 wk)	
Informed Consent	X																X[26]		
Polyposis History[1]	X																		
Medical History[24]	X		X		X				X				X				X	X[14]	
GI Symptoms	X		X		X				X				X				X	X[14]	
Surgical History	X																	X[14]	X[19]
Concomitant Medications	X	X[13]	X	X[13]	X	X[13]	X[13]	X[13]	X	X[13]	X[13]	X[13]	X	X[13]	X[13]	X[13]	X	X[14]	
Drug Compliance Review		X[13]	X	X[13]	X	X[13]	X[13]	X[13]	X	X[13]	X[13]	X[13]	X	X[13]	X[13]	X[13]	X		
Adverse Events		X[13]	X	X[13]	X	X[13]	X[13]	X[13]	X	X[13]	X[13]	X[13]	X	X[13]	X[13]	X[13]	X	X[14]	
Chemistry Panel[2]	X		X		X				X				X				X		
CBC[3]	X		X		X				X				X				X		
Urinalysis[25]	X		X		X				X				X				X		
Vital Signs[4]	X		X		X				X				X				X		
Physical Exam/Review of Systems[5]	X		X		X				X				X				X		
Audiometry[6]	X								X								X		
EKG[22]	X		X[23]		X				X				X				X		
Serum Preg. Test[7]	X		X		X		X[7]		X		X[7]		X		X[7]		X		
Dispense Medications[8]		X[8]	X		X		X[8]		X		X[8]		X		X[8]				
Subject Diary[9]		X	X		X		X		X		X		X		X				
Food Frequency Questionnaire[15]	X								X								X		
LGI Endoscopy[10]	X				X				X				X				X		
Normal Mucosa Biopsy[11]	X				X				X				X				X		
UGI Endoscopy[12]	X				X				X				X				X		
Pharmacokinetics Blood Samples			X[16]																
Pharmacogenomic Blood Sample	X[17]																		
Polyamine Urine Samples[18]	X				X				X				X				X		
HRQoL surveys[20]	X		X		X				X				X				X		

FAP Study Schedule Footnotes (Table 3)

Note: Shaded columns in subject schedule (Table 3) are protocol required in person visits.

1. Polyposis history: Family history, age onset, physician or self-prescribed NSAIDs for polyp control, frequency and extent of post-colectomy interventions; specific findings during the past two endoscopies.
2. Chemistry panel includes – electrolytes (Na, K, CL, CO_2), liver function tests (AST, ALT, Alkaline phosphatase, bilirubin), BUN/urea, creatinine.
3. CBC panel includes – hemoglobin, hematocrit, WBC, platelet count, automated differential.
4. Vital signs – temperature, blood pressure, pulse, respirations.
5. Physical Exam/Review of body systems (includes body system assessment - HEENT, hepatic, renal, genitourinary, reproductive, hematologic/immunologic, endocrine/metabolic, musculoskeletal, neurologic [i.e., grossly normal, walk into office, speech normal, no tremors, alert and oriented], dermatologic, cardiovascular, respiratory, gastrointestinal) – including height (baseline only), weight, vital signs.
6. Audiometry will need to be done using air conduction methodology (250, 500, 1000, 2000, 4000 and 8000 Hz).
7. Women of child-bearing bearing potential with no prior hysterectomy and pre-menopausal must use an effective contraception method and will have a serum pregnancy (HCG) done every 3 months while on study treatment (see Section 6.1, #11).
8. Medications and subject diaries will be dispensed to the subject every 3 months (month 0, 3, 6, 9, 12, 15, 18, and 21) in person or by special arrangements.
9. Subjects are to record in their 3-month diaries: medication use, presence of symptoms, and a self-assessment of presence of gross blood or melena.
10. Lower GI (LGI) endoscopy (proctoscopy or colonoscopy) will be done on all randomized subjects that have an intact colon or rectum/pouch.
11. During the LGI procedure, normal mucosal biopsy for polyamine analysis will be obtained at; screening/baseline, 6, 12, 18, and 24 months/EOT. For subjects with permanent ileostomy, endoscopy not required; normal mucosal biopsies are performed on the visible ileostomy stoma.
12. On-study Upper GI (UGI) endoscopy will be done on all randomized subjects that have a duodenum.
13. Monthly (± 7 days) phone/email contact by the study coordinator to follow-up on medication/drug compliance review, concomitant medications, and adverse events.
14. The follow-up will be done as phone call to the subject to review medical history, surgical history for any FAP-related surgical events, concomitant medications and adverse events.
15. A food frequency recall questionnaire will be administered at the screening/baseline, 12 and 24 month/EOT visits. US and Canada sites only.
16. A peripheral blood sample (5 mL, lithium heparin) will be collected at each of the following time points: pre-dose and 1, 2, 4 and 8 hours post dose.
17. A peripheral blood sample (10 mL, EDTA) will be collected at screening/baseline for pharmacogenomic analysis.
18. A random urine sample (15 mL minimum) will be collected at the screening/baseline, 6, 12, 18 and 24 month/EOT visits for polyamine analysis.
19. The follow-up will be done monthly as phone call to review endoscopic excisional procedures/surgical history for any FAP-related surgical events.
20. HRQoL surveys will include EORTC QLQ-C30 and QLQ-CR29, EQ-5D health utility index assessment, and modified Cancer Worry Scale. They will be collected at screening/baseline, 3, 6, 12, 18, and 24 month/EOT visits.
21. EOT visit will occur within 2 weeks off study treatment for any cause including completion of treatment at 24 months.
22. Subject needs to be in the supine position for 10 minutes prior to the EKG, including EKGs collected during PK sampling.
23. 2-EKGs will be done on the day PK samples are collected: 1) before pre-dose sample and prior to dose, and 2) before the 4 hr PK sample is obtained.
24. Medical history includes – standard review of major systems, with particular attention to cardiovascular, cerebrovascular, peripheral vascular, gastrointestinal and hearing issues. Interaction with outside physicians should be documented.
25. Urinalysis panel includes – color, clarity/appearance, specific gravity, pH, protein, glucose, ketones and blood.
26. Subjects completing the initial 24 month treatment without an FAP-related event and participating in the extension study must be consented at this visit. Go to Table 4, for month 24 additional extension procedures. For those subjects not participating in the extension study, this will be the end of treatment visit.

Table 4 - FAP Study Schedule (Treatment Extension to a Maximum of 48 Months)

	Mo. 24[21]	Mo. 25, 26	Mo. 27	Mo. 28, 29	Mo. 30	Mo. 31, 32	Mo. 33	Mo. 34, 35	M 36	Mo. 37-38	Mo. 39	Mo. 40-41	Mo. 42	Mo. 43-44	Mo. 45	Mo. 46-47	Mo. 48/EOT	FU 30 days Off-Study
Procedures		(± 1 wk)			(± 2 wks)	(± 1 wk)			(± 2 wks)	± 1 wk			(± 2 wks)	(± 1 wk)			(± 2 wks[17])	± 1 wk
Informed Consent	X																	
Medical History[19]					X				X				X				X	X[13]
GI Symptoms					X				X				X				X	X[13]
Surgical History																		X[13]
Concomitant Medications		X[12]	X[12]	X[12]	X	X[12]	X[12]	X[12]	X	X[12]	X[12]	X[12]	X	X[12]	X[12]	X[12]	X	X[13]
Drug Compliance Review		X[12]	X[12]	X[12]	X	X[12]	X[12]	X[12]	X	X[12]	X[12]	X[12]	X	X[12]	X[12]	X[12]	X	
Adverse Events		X[12]	X[12]	X[12]	X	X[12]	X[12]	X[12]	X	X[12]	X[12]	X[12]	X	X[12]	X[12]	X[12]	X	X[13]
Chemistry Panel[1]					X				X				X				X	
CBC[2]					X				X				X				X	
Urinalysis[20]					X				X				X				X	
Vital Signs[3]					X				X				X				X	
Physical Exam[4]					X				X				X				X	
Audiometry[5]									X								X	
EKG[18]					X				X				X				X	
Serum Preg. Test[6]			X[6]		X		X[6]		X		X[6]		X		X[6]		X	
Dispense Medications[7]	X		X[7]		X		X[7]		X		X[7]		X		X[7]			
Subject Diary[8]	X		X		X		X		X		X		X		X			
Food Frequency Questionnaire[14]									X								X	
LGI Endoscopy[9]					X				X				X				X	
Normal Mucosa Biopsy[10]					X				X				X				X	
UGI Endoscopy[11]					X				X				X				X	
Polyamine Urine Samples[15]					X				X				X				X	
HRQoL surveys [16]					X				X				X				X	

FAP Study Schedule Treatment Extension Footnotes (Table 4)

Note: Shaded columns in subject schedule (Table 4) are protocol required in person visits.

1. Chemistry panel includes – electrolytes (Na, K, CL, CO_2), liver function tests (AST, ALT, Alkaline phosphatase, bilirubin), BUN, creatinine.
2. CBC panel includes – hemoglobin, hematocrit, WBC, platelet count, automated differential.
3. Vital signs – temperature, blood pressure, pulse, respirations.
4. Physical Exam/Review of body systems (includes body system assessment - HEENT, hepatic, renal, genitourinary, reproductive, hematologic/immunologic, endocrine/metabolic, musculoskeletal, neurologic [i.e., grossly normal, walk into office, speech normal, no tremors, alert and oriented], dermatologic, cardiovascular, respiratory, gastrointestinal) – including height (baseline only), weight, vital signs.
5. Audiometry will need to be done using air conduction methodology (250, 500, 1000, 2000, 4000 and 8000 Hz).
6. Women of child-bearing bearing potential with no prior hysterectomy and pre-menopausal must use an effective contraception method and will have a serum pregnancy (HCG) done every 3 months while on study treatment (see Section 6.1, #11).
7. Medications and subject diaries will be dispensed to the subject every 3 months (month 24, 27, 30,33, 36, 39, 42, and 45) in person or by special arrangements.
8. Subjects are to record in their 3-month diaries: medication use, presence of symptoms, and a self-assessment of presence of gross blood or melena.
9. Lower GI (LGI) endoscopy (proctoscopy or colonoscopy) will be done on all randomized subjects that have an intact colon or rectum/pouch.
10. During the LGI procedure, normal mucosal biopsy for polyamine analysis will be obtained at months 30, 36, 42 and 48/EOT visits. For subjects with permanent ileostomy, endoscopy not required; normal mucosal biopsies are performed on the visible ileostomy stoma.
11. On-study Upper GI (UGI) endoscopy will be done on all randomized subjects that have a duodenum.
12. Monthly (± 7 days) phone/email contact by the study coordinator to follow-up on medication/drug compliance review, concomitant medications, and adverse events.
13. The follow-up will be done as phone call to the subject to review medical history, surgical history for any FAP-related surgical events, concomitant medications and adverse events.
14. A food frequency recall questionnaire will be administered at month 36 and 48/EOT visit. US and Canada sites only.
15. A random urine sample (15 mL minimum) will be collected at months 24, 30, 36, 42 and 48/EOT visits for polyamine analysis.
16. HRQoL surveys will include EORTC QLQ-C30 and QLQ-CR29, EQ-5D health utility index assessment, and modified Cancer Worry Scale. They will be collected at months 30, 36, 42 and 48/EOT visits.
17. EOT visit will occur within 2 weeks off study treatment for any cause including completion of treatment at 48 months.
18. Subject needs to be in the supine position for 10 minutes prior to the EKG.
19. Medical history includes – standard review of major systems, with particular attention to cardiovascular, cerebrovascular, peripheral vascular, gastrointestinal and hearing issues. Interaction with outside physicians should be documented.
20. Urinalysis panel includes – color, clarity/appearance, specific gravity, pH, protein, glucose, ketones and blood.
21. These procedures are in addition to those listed for Month 24 on the initial treatment schedule (Table 3).

8.2. Patient Accrual Logistics

8.2.1. Initial Visit – Determining Potential Eligibility

Based on general medical and polyposis history, prior surgery, cardiac risk assessment and clinical hearing loss, current aspirin and NSAID use - patients will be determined to be potentially eligible for this trial. After appropriate discussions, written informed consent will be obtained.

8.2.2. Subsequent Screening for Eligibility

If the patient has not already been genotyped for FAP, genetic analysis will be performed to confirm the presence of an APC mutation.

Lower GI Endoscopy: Patients will be evaluated via colonoscopy, flexible or rigid procto-sigmoidoscopy during the screening phase. Biopsies, ablations, and snare excisions at baseline are performed per the clinician's standard of care. If considered eligible based on inclusion criteria, a grossly normal mucosa biopsy will be obtained for baseline polyamine measurement. Still and video documentation of the colon (vide infra) or the residual rectum or entire pouch will also be obtained for archiving. Polyp size will be determined by visual comparison with biopsy forceps that can measure 5.0 – 5.5 mm in the fully open position. Procedural details are provided in the Investigator Manual. All randomized patients with an intact colon or rectum/pouch will have baseline and on-study lower GI endoscopy procedures as part of this trial.

Upper GI Endoscopy: The duodenum will be evaluated by forward-viewing and/or side-viewing gastroscopes (with still and video documentation with closed and open biopsy forceps near mucosa). Procedural details are provided in the Investigator Manual. All randomized patients with a duodenum will have baseline and on-study UGI endoscopy as part of this trial. Subjects stratified to the duodenal group must have duodenal biopsies of all polyps 1 cm or larger to determine HGD and histology required for determining Stage 3 or 4 Spigelman status.

A physical exam/review of body systems, height, weight and vital signs will be performed.

Baseline blood and urine tests within 30 days of randomization: Per eligibility criteria – CBC, chemistry profile, urinalysis, and a sample for pharmacogenomic and genetic analysis.

In order to ascertain how many patients with clinical FAP have baseline hearing deficits, patients meeting all the criteria for this trial will undergo air conduction audiometry. Results will not be relevant to eligibility.

8.2.3. Final Eligibility and Potential Screen Failures

If the patient has signed the informed consent, and all eligibility criteria are met, the subject will be randomized. Screening UGI, LGI and rectal/pouch images will be submitted to the central imaging laboratory for central collection and archiving. Quality of life questionnaires (EORTC QLQ-C30, EORTC QLQ-CR29, EQ-5D, and the modified Cancer Worry Scale) will be provided to the subject to complete to obtain baseline values. A food frequency questionnaire will be provided to the subject to complete for baseline values at North American (United States and Canada) sites only.

The patient may be a screen failure based on history, physical exam, genetic assessment, or other laboratory values. A screen failure case report form will need to be completed by the Investigator or study coordinator and available for review by the study Sponsor.

8.2.4. Drug Administration

After confirming eligibility, the patient will be randomized to one of the three treatment arms (Table 5). Randomization should be performed within 5 working days prior to the initiation of treatment. Specific procedures for randomization will be included in the study manual.

Table 5 - Study Medication Schedule[1]

AGENT and DOSE	ROUTE	RX INTERVAL
CPP-1X 750 mg & Sulindac 150 mg	Oral	Daily for up to 48 months
OR		
CPP-1X placebo & Sulindac 150 mg	Oral	Daily for up to 48 months
OR		
CPP-1X 750 mg & Sulindac placebo	Oral	Daily for up to 48 months

[1]The medications are to be taken at approximately the same time daily with food.
* Each CPP-1X tablet = 250 mg; ** Each sulindac tablet = 150 mg

The study medication and subject diaries will be dispensed to the subject at the initial treatment visit and at 3 month intervals thereafter in person or by special arrangement. Subjects will be instructed to take their medication with food at approximately the same time each day, preferably in the morning. The subject will be instructed to record dosing compliance on a weekly basis in the subject diary.

Based on published data utilized to project event rates, subjects will receive treatment for up to 48 months. However, interim analyses prescribed by the Data Monitoring Committee charter may result in earlier stopping based on futility or toxicity.

8.2.5. Initial 24-Month Treatment Intervention Assessments

Refer to Section 8.1, Table 3 and Table 4 for subject assessments and the treatment schedule for screening, on-study, end of treatment and follow-up visits.

During the initial 24-month drug intervention, subjects will be followed monthly by phone or in person visits interview for assessment of possible toxicities and medication compliance. A diary of compliance and symptoms will be maintained by subjects and reviewed during the next office visit. At each interval assessment visit (month 3, 6, 12, 18, and 24), until the subject completes 24 months of treatment or the subject comes off study treatment additional drug supplies and subject diaries will be provided.

At months 1, 2, 4, 5, 7, 8, 10, 11, 13, 14, 16, 17, 19, 20, 22, 23 ($\pm$ 1 week), a follow-up visit via phone contact will be performed to assess for side effects, other medications, to remind subjects to complete their diary and to continue to take their study medications.

At the 3-month visit ($\pm$ 1 week), subjects will have a physical exam/review of body systems (including weight and vital signs), blood and urine samples obtained for laboratory tests (CBC, chemistry panel, urinalysis), pharmacokinetics (PK), and EKGs (before the pre-dose sample, prior to drug administration and before the 4-hour PK sample collection. Subject needs to be in

the supine position for 10 minutes prior to the EKG). Women of child bearing potential will also have a serum pregnancy test performed. Concomitant medications, adverse events and medication compliance will also be reviewed. Quality of life questionnaires (EORTC QLQ-C30, EORTC QLQ-CR29, EQ-5D, and the modified Cancer Worry Scale) will be provided to the subject to complete.

At the 6-month and 18-month visits (± 2 weeks), subjects will have a physical exam/review of body systems (including weight and vital signs), blood samples obtained for laboratory tests (CBC, chemistry panel, urinalysis), a random urine sample will be obtained for polyamine determination, EKG (Subject needs to be in the supine position for 10 minutes prior to the EKG) and their first on study treatment upper and lower endoscopy procedures with image and video documentation will be obtained. A normal rectal/pouch mucosal biopsy for polyamine determination will be obtained during the colonoscopy/proctoscopy procedure. Women of child bearing potential will also have a serum pregnancy test performed. Concomitant medications, adverse events and medication compliance will also be reviewed. Quality of life questionnaires (EORTC QLQ-C30, EORTC QLQ-CR29, EQ-5D, and the modified Cancer Worry Scale) will be provided to the subject to complete. Study drug and diaries will be dispensed.

At the 9-month, 15-month and 21-month visits (± 1 week), subjects will have drug and diary dispensing. Women of child bearing potential will also have a serum pregnancy test performed. Concomitant medications, adverse events and medication compliance will also be reviewed.

At the 12-month and 24-month visits (± 2 weeks), subjects will have a physical exam/review of body systems (including, weight and vital signs), blood samples obtained for laboratory tests (CBC, chemistry panel, urinalysis), a random urine sample will be obtained for polyamine determination, audiometry testing, EKG (Subject needs to be in the supine position for 10 minutes prior to the EKG) and their second set of on study treatment endoscopy procedures with image and video documentation will be obtained. A normal mucosal biopsy for polyamine determination will be obtained during the colonoscopy/proctoscopy procedure. Women of child bearing potential will also have a serum pregnancy test performed. Concomitant medications, adverse events and medication compliance will also be reviewed. Quality of life questionnaires (EORTC QLQ-C30, EORTC QLQ-CR29, EQ-5D, and the modified Cancer Worry Scale) will be provided to the subject to complete. A food frequency questionnaire will be provided to the subject to complete at North American (United States and Canada) sites only. Study drug and diaries will be dispensed at 12-month and if the subject continues on the treatment extension at 24-month.

Subjects completing the initial 24 months of study treatment, without an FAP related event, and have completed the 24 month visit procedures as outlined below may be eligible to participate in the 24 month treatment extension (See Section 8.2.10). For those subjects that do not go on to the treatment extension, this will be the end of treatment visit. It must be documented in the subject's medical record why the subject declined participation in the treatment extension if they met the requirements for participation, see Section 8.2.10.

8.2.6. Initial 24 Month Treatment Intervention Early Termination (+ 2 weeks)

Within 2 weeks off final study pill treatment for any cause, all subjects will have a follow-up history and physical exam/review of body systems (including, weight and vital signs), along with toxicity assessment. Repeat blood laboratory tests (CBC, chemistry panel, and urinalysis), a random urine sample will be obtained for polyamine determination, EKG (Subject needs to be in the supine position for 10 minutes prior to the EKG) and audiometry will be performed. Women

of child bearing potential will also have a serum pregnancy test performed. Concomitant medications, adverse events and medication compliance will also be reviewed. Quality of life questionnaires (EORTC QLQ-C30, EORTC QLQ-CR29, EQ-5D and the modified Cancer Worry Scale) will be provided to the subject to complete. A food frequency questionnaire will be provided to the subject to complete at North American (United States and Canada) sites only.

Repeat upper and lower endoscopies with image and video documentation will be obtained at the Month 24/EOT visit or if the subject has completed at least 3 months of treatment from the previous on-study upper and lower endoscopy procedures (including baseline). A normal mucosal biopsy sample for polyamine determination will be obtained during the colonoscopy/proctoscopy procedure.

If the subject has an unscheduled upper/lower endoscopy for any reason, these procedures should be captured with image and video documentation including the collection of a normal mucosal biopsy, if possible. A random urine sample should be obtained for polyamine determination, if possible.

Subjects will be formally taken off-study treatment and complete the End of Treatment (EOT) assessments if there is a cumulative delay/suspension of study medication for any reason of:

- > 90 days from randomization to month 36
- > 105 days from randomization to month 42
- > 120 days from randomization to month 48

A temporary suspension from taking study medication as stated above (for example, due to a non-FAP disease related surgery or procedure), will be documented as a treatment delay and the subject will continue on study, on their original schedule.

8.2.7. Initial 24 Month Treatment Intervention Follow-Up (30-days post end of treatment visit +/- 1 week) Off Study

Thirty-days (30) after completion of the end of study evaluations, subjects will be contacted by phone for a clinical update in regard to symptoms and interval medical history. Concomitant medications and adverse events will also be reviewed. The subject will provide a clinical update and procedure date for any FAP-related surgical event or major endoscopic excisional event that has occurred since the last contact. These include partial colectomy, colectomy with IRA, total procto-colectomy, proctectomy, pouch resection, sub-mucosal resection, trans-duodenal excision, ampullectomy, duodenectomy, or Whipple procedure.

An FAP-related event at any disease site (colon/rectum/pouch, duodenum) will lead to discontinuation of the study treatment but follow-up of the subject will continue until the end of the 30 day follow-up period.

8.2.8. Initial 24 Month Treatment Intervention Follow-Up (Months 2-6, each month +/- 1 week) Off Study

For the next 5 months after the 30 day follow-up, if the subject went off study treatment for disease progression indicating the need for an any FAP-related surgical event or major endoscopic excisional event, and the surgical/endoscopic event had not yet occurred at the time of the 30 days post end of treatment visit, subjects will be contacted by phone to obtain the procedure date of any FAP-related surgical event or major endoscopic excisional event that has occurred since the last contact. These include partial colectomy, colectomy with IRA, total

procto-colectomy, proctectomy, pouch resection, sub-mucosal resection, trans-duodenal excision, ampullectomy, duodenectomy, or Whipple procedure.

8.2.9. Treatment Extension Intervention (Months 25 - 48)

Subjects completing the initial 24 months of study treatment, without an FAP related event, and have completed all the 24 month visit procedures as outlined in Section 8.2.6 and Table 3 and Table 4 may be eligible to participate in the treatment extension.

In order to participate, a subject must meet the following requirements:

1. Subject has completed 24 months of treatment without an FAP related event.
2. Subject has completed all the month 24 visit procedures.
3. Subject is no more than 14 days beyond the 24 month or 36 month visit.
4. Subject has signed the informed consent for treatment extension.

Once the above requirements are met, the subject will have drug and diary dispensed.

At months 25, 26, 28, 29, 31, 32, 34, 35, 37, 38, 40, 41, 43, 44, 46, and 47 (± 1 week), a follow-up visit via phone contact to assess for side effects, other medications, to remind subjects to complete their diary and to continue to take their study medications.

At the 27-month, 33-month, 39-month and 45-month visits (± 1 week), subjects will have drug and diary dispensing. Women of child bearing potential will also have a serum pregnancy test performed. Concomitant medications, adverse events and medication compliance will also be reviewed.

At the 30-month and 42-month visits (± 2 weeks), subjects will have a physical exam/review of body systems (including weight and vital signs), blood samples obtained for laboratory tests (CBC, chemistry panel, urinalysis), a random urine sample will be obtained for polyamine determination, EKG (Subject needs to be in the supine position for 10 minutes prior to the EKG) and their first on study treatment upper and lower endoscopy procedures. A normal rectal/pouch mucosal biopsy for polyamine determination will be obtained during the colonoscopy/proctoscopy procedure. Women of child bearing potential will also have a serum pregnancy test performed. Concomitant medications, adverse events and medication compliance will also be reviewed. Quality of life questionnaires (EORTC QLQ-C30, EORTC QLQ-CR29, EQ-5D, and the modified Cancer Worry Scale) will be provided to the subject to complete.

At the 36-month, and 48-month visits (± 2 weeks), subjects will have a physical exam/review of body systems (including, weight and vital signs), blood samples obtained for laboratory tests (CBC, chemistry panel, urinalysis), a random urine sample will be obtained for polyamine determination, audiometry testing, EKG (Subject needs to be in the supine position for 10 minutes prior to the EKG) and their second set of on study treatment endoscopy procedures. A normal mucosal biopsy for polyamine determination will be obtained during the colonoscopy/proctoscopy procedure. Study drug and diaries will be dispensed at 36-month if eligible to continue. Women of child bearing potential will also have a serum pregnancy test performed. Concomitant medications, adverse events and medication compliance will also be reviewed. Quality of life questionnaires (EORTC QLQ-C30, EORTC QLQ-CR29, EQ-5D, and the modified Cancer Worry Scale) will be provided to the subject to complete. A food frequency questionnaire will be provided to the subject to complete at North American (United States and Canada) sites only.

8.2.10. Treatment Extension - End of Treatment/Early Termination (+/- 2 weeks)

Within 2 weeks of final study pill treatment for any cause, all subjects will have a follow-up history and physical exam/review of body systems (including, weight and vital signs), along with toxicity assessment. Repeat blood laboratory tests (CBC, chemistry panel, and urinalysis), EKG (Subject needs to be in the supine position for 10 minutes prior to the EKG) and audiometry will be performed. Women of child bearing potential will also have a serum pregnancy test performed. Concomitant medications, adverse events and medication compliance will also be reviewed. Quality of life questionnaires (EORTC QLQ-C30, EORTC QLQ-CR29, EQ-5D and the modified Cancer Worry Scale) will be provided to the subject to complete. A food frequency questionnaire will be provided to the subject to complete at North American (United States and Canada) sites only.

Repeat upper and lower endoscopies with image and video documentation will be obtained at the end of treatment visit if the subject has completed at least 3 months of treatment from the previous on-study upper and lower endoscopy procedures (including month-24). A normal mucosal biopsy will be obtained during the colonoscopy/proctoscopy procedure and a urine sample will be collected for polyamine determination.

If the subject has an unscheduled upper/lower endoscopy for any reason, these procedures should be captured with image and video documentation including the collection of a normal mucosal biopsy, if possible. A random urine sample should be obtained for polyamine determination, if possible.

8.2.11. Treatment Extension Follow-Up (30-days post end of treatment visit +/- 1 week) Off Study

Thirty-days (30) after completion of the treatment extension evaluations, subjects will be contacted by phone for a clinical update in regard to symptoms and interval medical history. Concomitant medications and adverse events will also be reviewed. The subject will provide a clinical update and procedure date for any FAP-related surgical event or major endoscopic excisional event that has occurred since the last contact. These include partial colectomy, colectomy with IRA, total procto-colectomy, proctectomy, pouch resection, sub-mucosal resection, trans-duodenal excision, ampullectomy, duodenectomy, or Whipple procedure.

An FAP-related event at any disease site (colon/rectum/pouch, duodenum) will lead to discontinuation of the study treatment but follow-up of the subject will continue until the end of the 30 day follow-up period.

8.2.12. Termination of Treatment Extension Procedures

Subjects on the treatment extension can continue on treatment for up to 48 months based on their date of randomization as follows:

1. If randomized between November 2015 and April 2016 eligible for up to 36 months
2. If randomized between May 2015 and October 2015 eligible for up to 42 months
3. If randomized between July 2014 and April 2015 eligible for up to 48 months

or until one of the following occurs:

1. Subject has an FAP-related event or comes off study for other reasons
2. Trial end-date of April 30, 2019 has been reached

3. 90 FAP-related events have occurred
4. Less than 90 FAP-related events have accrued prior to April 30, 2019 and an earlier trial end-date has been set by the Sponsor and reviewed by the DMC
5. An earlier trial end date prior to April 30, 2019 has been recommended by the DMC for safety reason and approved by the Sponsor.

8.2.13. Treatment Compliance

Subjects will be formally taken off-study treatment and complete the End of Treatment (EOT) assessments if there is a cumulative delay/suspension of study medication for any reason of:

- > 90 days from randomization to month 36
- > 105 days from randomization to month 42
- > 120 days from randomization to month 48

8.2.14. Definition of FAP-Related Events or Serious and Unexpected Toxicity

The time from the date of randomization to the date of the first occurrence of any FAP-related event at any disease site (colon/rectum/pouch, duodenum) will lead to discontinuation of the study treatment. Follow-up of the subject for FAP-related events will continue, per protocol, until the end of the 30 day post-treatment.

FAP-related primary events by disease site are as follows:

1. Pre-operative, intact colon:
   a) Disease progression^ indicating need for colectomy with IRA or total procto-colectomy

2. Rectum or pouch events include one or more of the following:
   a) Excisional intervention by surgical snare or trans-anal excision to remove any polyp ≥ 10 mm in size (per pathology report) and/or pathologic evidence of high grade dysplasia.*
   b) Disease progression^ indicating need for proctectomy
   c) Disease progression^ indicating need for pouch resection
   d) Development of cancer in rectum or pouch
   e) Death

3. Duodenal disease includes the following:
   a) Progression in Spigelman Stage to more advanced stage (Stage 2, 3 or 4), refer to Appendix A
   b) Disease progression indicating need for excisional intervention (sub-mucosal resection, trans-duodenal excision, ampullectomy, duodenectomy, Whipple procedure)
   c) Development of cancer
   d) Death

Note, excisional intervention may include open surgery, trans-anal surgery or endoscopic excisions/snare but does not include cautery ablations or hot biopsy.

*For those subjects stratified to the duodenal group, all concurrent rectal pouch polyps > 5 mm must have been removed at baseline for this event to apply.

^Disease progression is based on endoscopic evaluations compared to baseline demonstrating a clinically significant increase in number and/or size of polyps (~25% increase in disease burden), presence of a large sessile or ulcerated adenoma not amenable to removal, high grade dysplasia in any adenoma, or in-situ or invasive cancer.

Discontinuation from study treatment due to a potential treatment related serious adverse event may include the following:

- Gastrointestinal hemorrhage, ≥ grade 3
- Tinnitus ≥ grade 2, or clinical hearing impairment ≥ grade 3
- Cardiovascular events include cardiac arrest, cardiac-chest pain, myocardial infarction, thromboembolic event, phlebitis (deep or superficial), and spontaneous abdominal wall or retroperitoneal hematoma at least 10 cm in maximum dimension.
- Grade ≥ 3 Cardiac ischemia/infarction or cerebrovascular ischemia, whether related to study drug or not.

Adverse events and serious adverse events must be recorded carefully and completely on the case report forms and SAE report forms. Adverse event reporting and grading will be done using the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03.

If a subject comes off study treatment for any of the above listed FAP or SAE events, the subject will need to complete all tests, procedures and assessments required at the Final Intervention/End of Treatment visit, including 30-day follow-up.

All subjects who go off study treatment due to an FAP-related event, toxicity, or intercurrent illness, or who withdraw consent for further treatment will be followed for at least 30 days from their last dose of study medication.

8.3. Study Blinding Information and Criteria for Protocol Treatment Removal

8.3.1. Blinding and Unblinding

Treatment will be provided in a double blind manner such that neither the subject, Investigator, clinic staff nor the Sponsor will know which combination is being administered. Randomization numbers will be assigned based on information obtained from an interactive web-based response system.

Subject treatment will be unblinded in emergency situations by the study Investigator if it is in the best interest of the trial subject in order to provide medical care to the subject and includes medical decisions such as whether to start or stop treatment or institute alternative treatment if required. Specifically, we expect that unblinding of an individual study subject's treatment assignment may occur if in the opinion of the Investigator that the identification of the study medication is necessary to protect the welfare of the subject. The study drug may be discontinued without unblinding the participant.

If the blind is prematurely broken for a subject, it is the responsibility of the Investigator to promptly document and explain any unblinding to Cancer Prevention Pharmaceuticals within 24 hours of the blind being broken.

Unblinding of subject treatment is done via the IWRS by the Investigator. If the Investigator is unable to access IWRS, the Drug Safety Group at Chiltern should be contacted at 1-919-468-2288 (US) and 001-919-468-2288 (EU) for a subject's treatment code.

8.3.2. Protocol Treatment Withdrawal (Off-Study Treatment)

Participants will be withdrawn from protocol treatment under the following circumstances:

1. Evidence of an FAP-related event as defined in Section 8.2.14.
2. Clinical reduction in hearing acumen requiring use of a hearing aid.
3. Grade ≥ 3 cardiac ischemia/infarction or cerebrovascular ischemia, whether related to study drug or not.
4. Pregnancy while on treatment, see Section 11.8.
5. Intercurrent illness which would, in the judgment of the treating physician, affect assessments of clinical status to a significant degree and/or require discontinuation of drugs. Participants will not discontinue study drugs for other medical events which are not considered to be treatment related. This determination will be made by the treating physician.
6. Cumulative delay of study intervention for any reason as follow:
    - > 90 days from randomization to month 36
    - > 105 days from randomization to month 42 or
    - > 120 days from randomization to month 48

    The first day of study treatment initiation is the randomization date regardless of study visit and/or procedure delays.
7. Completion of treatment intervention.
8. At the request of the Sponsor in situations such as protocol violations or concerns about the subject's safety.
9. The subject is lost to follow-up.
10. The subject may withdraw from the study-treatment at any time for any reason.
11. Subject death.

8.3.3. Protocol Withdrawal (Off-Study)

1. The subject may withdraw from the study at any time for any reason.

9. DISEASE ASSESSMENT AND SAMPLE COLLECTION

9.1. Baseline Endoscopy

A. Colon, Rectal, Pouch Assessment

Colonoscopy or flexible sigmoidoscopy will be used to assess the colon, rectum or the neo-rectum (ileal pouch) and video images captured for archiving and subsequent review. The last images will be retroflexed pictures of the distal rectum or pouch at the anorectal ring. One pass will be performed. Further details will be provided in the Imaging Manual.

Rectal/Neorectal Pouch

The entire residual rectum or pouch will be video-captured three times by:

- Advancing flexible scope to ileo-rectal anastomosis or proximal pouch. After advancement, the scope will be "twirled" to visualize all walls of the bowel as it is withdrawn.

- Retroflexed views of the distal rectum will be obtained at each visualization.
- Images of the bowel will be obtained using biopsy forceps in the fully open position placed near the mucosa.

Rectal/Neorectal Pouch Enumeration and Measurement

- Number of polyps in the rectum or pouch
- Endoscopic estimation of polyp size will be determined by visual comparison to a biopsy forceps that can measure, 5.0 - 5.5mm in the fully open position.
    - Number of polyps between 5 – 10 mm
    - Number of polyps > 10 mm
- All rectal/pouch polyps > 5 mm in diameter must be excised at baseline if the subject will be stratified to the rectum/pouch group. For details concerning subjects stratified to the rectal/pouch polyposis group (with or without involvement of the duodenum) please see Section 6.1, #4. For details concerning subjects stratified to the duodenal polyposis group (with or without involvement of rectum/pouch at stratification) please see Section 8.2.14.

Smaller polyps may be ablated per the treating institutions standard of care and three additional sets of video images will then be obtained as "baseline".

B. Duodenal Assessment

Duodenal assessment will use a forward and/or side-viewing endoscope with video images captured for subsequent review. The Spigelman classification (Appendix A) at screening will be utilized to stage the initial extent of disease and assess subject eligibility. A side-viewing scope may be used to improve assessment of the ampulla of Vater/papilla. Ampullary biopsies (with histology) and snare excisions will be performed per the protocol, Investigator Manual, and the institution's standard of care and the results of these procedures will be used as the subject's baseline Spigelman classification. Further details will be provided in the Imaging Manual.

The screening stage will be the initial Spigelman Stage (extent of polyposis combined with histology) and **the baseline** Spigelman Stage will be the post-snare intervention.

9.2. Follow-up Endoscopies

At six month intervals (+/- two weeks) – per Section 8.1, subjects will undergo repeat upper and lower endoscopy. At any interval assessment, if any subject requires an excisional intervention (as defined in Section 8.2.14), or has duodenal Spigelman stage progression (Stage 2, 3 or 4), the subject will be considered to have an FAP-related event and will come off study treatment.

9.3. Imaging Submission

All de-identified images will be captured on DVD or flash drive, de-identified, and forwarded to a central imaging laboratory for archiving. All data will be de-identified in regard to subject, site and treatment but subject study ID number will be available for baseline and subsequent comparison as appropriate. Post-hoc global assessment by blinded reviewers not involved in this trial will perform the assessment - using a 5 point scale - much less, somewhat less, none or minor changes, somewhat worse, much worse. This process will be defined in detail and included in the imaging manual for still and video endoscopy image submission.

9.4. Population Pharmacokinetic Sampling

All subjects will have blood samples obtained for pharmacokinetic studies. Pharmacokinetic sampling will occur once at the scheduled 3-month visit. Samples may be collected within ± 1 weeks of this visit. These visits start in the morning, to allow for subjects to hold their morning study medication dose, and for samples to be taken during standard working hours.

The subject will be contacted by a study coordinator at least three (3) days prior to the scheduled visit to remind the subject to not take their morning dose of study medication on the day of the planned visit.

On the morning of the visit, upon subject arrival, it will be verified that the subject did not take their morning dose of study medication. Those subjects that mistakenly took their morning dose will be sent home and rescheduled within the next week.

Prior to the pre-dose blood sample collection, a resting EKG will be obtained (subject needs to be in the supine position for 10 minutes prior to the EKG). After the EKG was obtained, a pre-dose blood sample (5 mL, lithium heparin vacutainer tube) will be collected.

The subject will then take their study medications in the usual manner. The subject may then leave the clinic and have their typical breakfast. Subjects will be asked to note the time breakfast was finished, as that will be recorded.

Table 6 – Pharmacokinetic Sample Number, Sampling Times and EKG collection

Sample Number	Target Time	No Earlier Than	No Later Than
	EKG – Prior to pre-dose sample collection and drug administration		
1	Pre-dose*	NA	NA
2	1 hour post dose	45 minutes	75 minutes
3	2 hours post dose	90 minutes	150 minutes
	EKG – Prior to 4 hour sample collection		
4	4 hours post dose*	3 hours	5 hours
5	8 hours post dose	6 hours	10 hours

*EKGs need to be done **1) before** the pre-dose sample and before drug administration and **2) before** the 4 hour samples are collected.

Post dose blood samples will be collected (5 mL each) at 1, 2, 4, and 8 hours following the morning dose of study medication (see Table 5). Deviations around these sample times should be no more than ± 15 minutes, ± 30 minutes, ± 60 minutes (1 hour), ± 120 minutes (2 hours), respectively, keeping in mind that the **fourth and fifth samples** must be at least one hour apart.

At the 4 hour time point and prior to the 4 hour blood sample collection, a resting EKG will be obtained (subject needs to be in the supine position for 10 minutes prior to the EKG). After the EKG is obtained, the 4 hour time point blood sample (5 mL, lithium heparin vacutainer tube) will be collected.

On the pharmacokinetic sampling case report form page, study coordinators will record the time of the pre-dose blood sample and the time breakfast was finished. Also, the relative ideal blood

sampling times (relative to dose time), and the actual blood sampling times will be recorded. Missed samples or samples collected outside of the time windows will still be stored and analyzed. Collected blood samples will be processed, stored, and shipped to a central laboratory according to procedures provided in the study manual.

Plasma concentration data from this trial will be pooled with data from other clinical trials, when available, for analysis. For each drug, a database will be constructed that includes the nominal and recorded dosing history, plasma analyte concentrations, demographic (body size, age, race, gender) data, laboratory data (hepatic and renal function), medical history (colonic resection), and clinical trial identifier. These data will be analyzed using methods appropriate for sparse data (mixed-effects modeling using NONMEM).

9.5. Polyamine Sample Collection (Normal Mucosa Biopsy, Random Urine Sample)

Subject tissue samples will undergo a baseline polyamine assay (examination of grossly normal rectal mucosal cup forcep biopsy and random urine sample - minimum 15 mL) pre-treatment, as a component of the screening process, and at each endoscopy/proctoscopy evaluation. Collected tissue and urine samples will be processed, stored, and shipped to a central laboratory according to procedures provided in the study manual.

For subjects who have signed the Optional Research Use of Biospecimens portion of the informed consent, left over urine or tissue samples may be used for exploratory assessment of levels of expression of RNA, proteins, or other molecules, such as polyamines, in the polyamine synthesis pathway, the APC signaling pathway, and other related pathways. Analysis may include mutation status for genes involved in the polyamine synthesis pathway, APC pathway, or other FAP related pathways.

9.6. Pharmacogenomic and Genetic Testing Sample Collection

Subjects will have 10 mL of peripheral blood collected in an EDTA vacutainer tube during their baseline/screening visit for subsequent correlative science research. Collected blood samples will be processed and shipped to a central laboratory according to procedures provided in the study manual.

For subjects who have signed the Optional Research Use of Biospecimens portion of the informed consent, left over blood samples may be used for exploratory assessment of levels of expression of RNA, proteins, or other molecules, such as polyamines, in the polyamine synthesis pathway, the APC signaling pathway, and other related pathways. Analysis may include mutation status for genes involved in the polyamine synthesis pathway, APC pathway, or other FAP related pathways.

10. QUALITY OF LIFE AND DIETARY ASSESSMENTS

10.1. Assessment of Quality of Life and Subject Preferences

For this study, we plan to use four (4) instruments to measure HRQoL and subject preferences or utilities. These instruments include the EORTC QLQ-C30, EORTC QLQ-CR29, EQ-5D, and a modified Cancer Worry Scale.

- The EORTC QLQ-C30 is a self-administered quality of life questionnaire[70] with multi-dimensional scales. It consists of both multi-item scales and single item measures, including five functioning domains, a global quality of life domain, three symptom domains and six single items.
- The EORTC QLQ-CR29 gastrointestinal / colorectal sub-module[71] is composed of 4 functional and 18 symptom related sub-scales. The 4 functional scales include body image, weight, anxiety and sexual function. The symptom related scales include single item and multi-item questions concerning stool frequency, bleeding and mucous discharge, stool leakage, abdominal bloating, flatulence, embarrassment and site-specific pain among others.
- The EuroQol EQ-5D is a standardized instrument for use as a measure of health outcome and is applicable to a wide range of health conditions and treatments.[72,73] It provides a simple descriptive profile and a single index value for health status.
- The Cancer Worry Scale[74] is a brief psychometric instrument that was designed to assess both the frequency of worrying about "getting cancer some day" and measuring the impact of worry on mood and performing daily activities. This scale was originally developed by Caryn Lerman and her colleagues to study breast cancer and has been modified for use in this FAP trial.

The validity and reliability of both the QLQ-C30 and the QLQ-CR29 questionnaires have been studied by the EORTC Study Group on Quality of Life and both instruments will be scored according to the EORTC Scoring Manual and analyzed accordingly.

HRQoL measures will be obtained at baseline, month 3, at every interim endoscopy visit, and at end of treatment. For each single item or multi-item sub-scale, a linear transformation will be applied to standardize raw scores to range between 0 and 100. HRQoL secondary endpoints will include all single item or multi-item sub-scales from both the EORTC QLQ-C30 and QLQ-CR29 and subjects will be considered as deteriorated (or improved) for a given single item or multi-item sub-scale if their change score from baseline was 10 points or more on the standardized scale.

In addition to the HRQoL assessment, subject preferences (or utilities) will also be assessed. Data will be collected at baseline, month 3, at every interim endoscopy visit, and at end of treatment and preference weights among the treatment arms will be determined using the EuroQol EQ-5D assessment of individual health states.[72,73] Quality-adjusted survival among the three treatment arms will be generated by multiplying the utility value by the amount of time spent in a specified health state.

The modified version of the Cancer Worry Scale will also be administered at baseline, month 3, at every interim endoscopy visit, and at end of treatment and it will be scored according to the guidance provided by Lerman *et al*.[74]

10.2. Dietary Assessment

The Food Frequency Questionnaire (FFQ) is the most common dietary assessment tool used in large epidemiologic studies of diet and health. The self-administered FFQ booklet asks participants to report the frequency of consumption and portion size of approximately 125 line items over a defined period of time (e.g. the last month; the last three months). Each line item is defined by a series of foods or beverages. Additional questions on food purchasing and preparation methods enable the analysis software to further refine nutrient calculations. The FFQ was developed by the Nutrition Assessment Shared Resource (NASR) of the Fred Hutchinson Cancer Research Center. NASR periodically updates its standard FFQ to reflect U.S. food consumption patterns and major changes in the market place.[82,83] Data from the FFQ will be analyzed using a polyamine database[69] and will calculate the average daily levels of putrescine, spermidine, and spermine in the diet. Dietary assessments via the FFQ will be obtained at baseline, months 12, 24, 36 and 48/end of treatment for subjects at North American (U.S. and Canada) sites only. The results of the FFQ will be used to corroborate results from another recent trial[84] that indicate consumption of a diet high in polyamines is associated with reduced treatment efficacy. The results of this trial along with the earlier findings of Zell *et al*[40] could lead to dietary restrictions in combination with the combined eflornithine-sulindac therapy.

11. ASSESSMENT OF SAFETY

11.1. Cardiac Risk

All subjects will undergo a baseline medical history evaluation and EKG for cardiovascular disease risk assessment. Subjects with cardiovascular risk factors as defined in Section 6.2 are not eligible for study participation. On-study cardiac risk assessments, for each subject, will take place throughout the study via ongoing adverse event assessments and periodic EKG evaluations at baseline, and months 3, 6, 12, 18, 24, 30, 36, 42 and 48/end of treatment.

11.2. Ototoxicity Risk

All subjects will undergo air conduction audiometry for hearing impairment as part of the screening process and at months 12, 24, 36 and 48/end of treatment. Subject diaries will indicate the presence of symptoms and will instruct the subject to contact the treating doctor for assessment. These data will not be used to exclude subjects from this study.

At months 3, 6, 12, 18, 24, 30, 36, 42 and 48/end of treatment, the subject will undergo a clinical assessment for ototoxicity adverse events symptoms by the research nurse or other medically qualified individual.

11.3. Gastrointestinal Risk

Subject's diaries will indicate presence of symptoms and will instruct the subject to contact the treating doctor for assessment. Stool will be self-assessed by subjects to determine if gross blood or melena is present. If so, treating doctor will be contacted and the subject assessed. Subject will perform stool assessments, which will be recorded in their diary.

At months 3, 6, 12, 18, 24, 30, 36, 42 and 48/end of treatment, the subject will undergo a clinical assessment for gastrointestinal adverse events symptoms by the research nurse or other medically qualified individual.

11.4. Safety Parameters

Subjects will be followed for safety from the start of treatment through 30 days after treatment discontinuation. Serious adverse events will be followed until resolved or returned to baseline, even if longer than 30 days from the subject's off study treatment or off study date.

Adverse events and serious adverse events must be recorded carefully and completely on the case report forms and SAE report forms. Adverse event reporting and grading will be done using the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03, (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf).

Serious adverse events must be reported to the Institutional Review Board (IRB)/Independent Ethics Review Committee (IEC)/Research Ethics Board (REB) by the Investigator and to regulatory authorities (FDA, National Health Authorities) by the Sponsor, according to established policy and regulatory requirements. Adverse events will also be coded to an organ system class. Summaries of safety data will be completed for the study population.

11.5. Adverse Events

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related (FDA definition) and is defined by the EU and Canadian regulations as any untoward medical occurrence in a subject or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug and from any route of administration, formulation, or dose, including overdose.

An adverse reaction means any adverse event caused by the drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

An adverse event does not include: pre-existing disease, conditions, or laboratory abnormalities present at the start of the study that do not worsen in frequency or intensity; situations where an untoward medical occurrence has not occurred (e.g., hospitalizations for cosmetic or elective surgery or social/convenience admissions); the disease being studied or signs or symptoms associated with the disease unless more severe than expected for the subject's condition.

For the FDA, an unexpected adverse event is an event that is not listed in the Investigator's Brochure (IB) at the specificity or severity observed or is mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but not mentioned as occurring with the drug(s) under investigation.

The Reference Safety Information (RSI) is located in the IB Ver. CPP-201-IB08 and subsequent versions, which is to be used for the purposes of determining expectedness and SAE/SUSAR reporting.

11.6. Serious Adverse Events

A serious adverse event determined by the opinion of the Investigator or Sponsors is defined as

1. Death;
2. A life-threatening event (places the subject at immediate risk of death);
3. Requires in subject hospitalization or prolongs hospitalization;
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
5. Congenital anomaly/birth defect;
6. Important medical events (IMEs) may be considered serious when, based on medical judgment, they may jeopardize the subject and require intervention to prevent one of the above serious outcomes.

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more serious form, might have caused death.

11.7. Reporting of AEs, SAEs, Serious and Unexpected Adverse Experiences

Subject Reporting of an Adverse Event

Subjects will be instructed to contact the Investigator or Research Nurse to report any symptom. The Investigator will question each subject regarding symptoms at the time of each physical examination/review of body systems. All adverse experiences, including duration and severity will be captured in the Case Report Forms provided by the Sponsor.

All adverse events are to be documented from the day the subject receives his/her first study treatment through 30 days after the subject's off study treatment date (date of last dose).

Reporting Serious Adverse Events (SAEs) to Sponsor

Serious Adverse Events are to be documented and reported to the Sponsor from the day the subject receives his/her first treatment through 30 days after the subject's off study treatment date. SAE follow-up needs to continue until the event is resolved or returned to baseline. Serious Adverse Events occurring to a subject after the 30-day off study treatment date should be reported to the Sponsor only if the SAE could be attributed to study treatment.

An Investigator shall report to the Sponsor via telephone, fax or e-mail, any Serious Adverse Event regardless of causality, within 24 hours of receipt of information.

Reporting to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Research Ethics Board (REB)

SAE's must be reported to the IRB/IEC/REB by the Investigator according to each institution's policy and procedures.

Reporting to Regulatory Authorities and Participating Investigators

The Sponsor will notify appropriate regulatory authorities by fax, telephone or in writing of any unexpected fatal or life-threatening suspected adverse reaction associated with the use of the

study drug as soon as possible, but in no event later than 7 calendar days after initial receipt of the information.

The Sponsor shall notify appropriate regulatory authorities and all participating Investigators in writing via IND safety reports/CIOMS reports of any serious and unexpected adverse experience associated with the use of the drug; and such reports shall be made as soon as possible but in no event later than 7 or 15 calendar days after the Sponsor's initial receipt of the information, depending on the reporting requirements.

The Sponsor will submit IND safety reports/CIOMS reports to FDA, Heath Canada, EMA, and National Competent Authorities as required, and all participating Investigators no later than 7 or 15 calendar days after the Sponsor determines that the suspected adverse reaction or other information qualifies for expedited reporting based on country specific regulatory requirements. If any regulatory authority requests any additional data or information, the Sponsor will submit it as soon as possible, but no later than 15 calendar days after receiving the request.

The Sponsor will report all adverse experiences to the U.S. FDA in Annual Reports to the IND, and to all applicable regulatory authorities annually as required, in addition to the final report of the clinical trial.

11.8. Reporting of Pregnancy

If following initiation of study treatment, it is discovered that:

- A female subject is pregnant or may have become pregnant at the time of investigational drug exposure, the investigational drug will be immediately discontinued until further assessment. If it is determined that study drug should be permanently discontinued, all study required procedures for study discontinuation and follow-up must be completed unless contraindicated by the pregnancy.
- For male subjects, if their partner is pregnant or may have become pregnant, the male subject must agree to the use of a barrier birth control method as stated in section 6.1 #11 *[Male subjects (including men who have had vasectomies) whose partners are pregnant should use condoms while the partner is pregnant. If the partner is still pregnant when the subject goes off study, the subject should continue condom uses for at least 2 weeks afterwards]*. If he does not agree to the above, he will be terminated from the study and all study required procedures for study discontinuation and follow-up must be completed.

The Investigator must notify the Medical Monitor within 24 hours of learning of the pregnancy and record the pregnancy on the Pregnancy Reporting Form and submit it to Cancer Prevention Pharmaceuticals via fax or email.

The Investigator must report using the Pregnancy Reporting Form, follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Generally, infants should be followed for a minimum of 6-8 weeks but additional follow up is not needed when a newborn is healthy.

Pregnancy itself is not considered an AE or SAE but any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE and reported as described in Sections 11.4 - 11.8.

11.9. Concomitant Medications

All concomitant medications and medications taken within 30 days before the first study drug administration until the subject's off study treatment date, and concomitant medications for AEs

recorded within the 30-days post-EOT, will be coded to therapeutic drug classes and generic names using, for example, the WHO Drug classification dictionary.

Subjects are to be instructed to not take the following medications or supplements while on study treatment: oral corticosteroids (such as prednisone), NSAIDS (such as ibuprofen, celecoxib, aspirin in excess of 700 mg weekly), diflunisal, supplements containing omega-3-fatty acids (such as fish oil), anticoagulants (such as warfarin, Pradaxa®, Eliquis®, Plavix®, and other direct thrombin inhibitors), fluconazole, lithium, furosemide and thiazides, DMSO, methotrexate, probenecid, propoxyphene hydrochloride, Tylenol® (acetaminophen) preparations containing aspirin or cytotoxic chemotherapy drugs.

12. STATISTICAL CONSIDERATIONS

The Statistical Analysis Plan (SAP) will focus on analysis of the primary and secondary endpoints, in order to assess the extent to which the combination of CPP-1X 750 mg daily + 150 mg sulindac is more effective than each agent alone in delaying the time from the date of randomization to the date of the first occurrence of any FAP-related event in Familial Adenomatous Polyposis (FAP) patients. Eligible patients who have given informed consent will enter the study with the intent to participate for the full treatment period. Accrual is expected to take 12-24 months. Eligible patients who have given informed consent will enter the treatment extension phase with the intent to participate for the full study extension treatment period of up to an additional 24 months.

The Statistical Analyses Plan will include method descriptions and will pre-specify the statistical approaches to be used, primary and secondary study endpoints, data handling conventions and randomization processes.

At least 150 eligible patients will be enrolled in this study, with at least 50 per treatment group. Patients will be randomized to one of three treatment groups within the prognostic strata defined in Section 4.3 in equal proportions (i.e., 1:1:1 randomization): 1) CPP-1X plus sulindac, 2) CPP-1X placebo plus sulindac, 3) CPP-1X plus sulindac placebo.

The study is double blinded, so neither subjects nor Investigator nor Sponsor will be aware of treatment assignment.

For the primary efficacy analyses, we will use the intent-to-treat (ITT) population defined as all subjects that have been randomized to one of the three study arms. Subjects will be analyzed in the group to which they were randomized, whether or not they received their assigned treatment, any treatment whatsoever, or completed their treatment course and follow-up. The safety outcome will be analyzed using all subjects in the ITT population who received at least one dose of study drug (safety population).

12.1. Primary Efficacy Objective and Analysis

The primary objective of this trial is to determine whether the combination of CPP-1X + sulindac is superior to either single-agent treatment individually in delaying the time from the date of randomization to the date of the first occurrence of any FAP-related event. Section 8.2.14 provides complete detail on FAP-related events.

Thus the primary objective contains two treatment comparisons:

1. CPP-1X placebo + sulindac active vs. CPP-1X active + sulindac active,

   and

2. CPP-1X active + sulindac placebo vs. CPP-1X active + sulindac active

These two treatment comparisons will be performed sequentially as described below.

The combination of CPP-1X active + sulindac active is specified as the reference treatment group because it is common to both comparisons. In addition, because the purpose of the combination treatment is to delay the time from randomization to FAP-related disease progression compared to single-agent treatments, formulating the hypothesis tests in this manner will allow a positive rather than a negative *Z*-score for the test statistic to be interpreted as supportive of this purpose.

Each comparison will be performed at the 2-sided 0.05 level of statistical significance.

As explained in the Statistical Analysis Plan, the decision to seek regulatory approval based upon the results of the primary objective will be taken sequentially.

CPP will sequentially perform the two primary comparisons as part of the primary analysis, each at the 2-sided p = 0.05 level. All information concerning these comparisons will be clearly provided to both Agencies. The single treatment comparison requested by FDA will be available, as will the two comparisons requested by EMA, both at the requested level of alpha. This approach fulfills the differing requirements for the primary comparison as asked for by each Agency.

We note that this approach is both a fixed-sequence and gatekeeping approach. It is fixed-sequence in that the comparison of combination with single-agent Sulindac takes place before the comparison of combination with single-agent Eflornithine and the first serves as a gatekeeper for the second (i.e., no declaration of significance in the second comparison will be made if the first comparison is not significant at the 0.05 level). Therefore, the type I error in the sequential testing is well controlled. In addition, because both tests must be significant for EMA approval, the type I error of the second test in the sequence is less than 0.05.

The analytic method for the primary analysis will be a time-to-event analysis using the stratified log-rank test. The stratified Cox proportional hazards regression models will be used for secondary assessments.[85] Graphical analyses (log-minus-log plots) will be used to check the assumption of constant hazard ratios. For the primary analysis, two stratified log-rank tests will be performed with treatment coded as a binary value (i.e., 0 or 1). Time to event curves will be displayed using the method of Kaplan and Meier[86]. Additional analyses involving the overall 3-treatment group comparison and use of additional study populations or the two pairwise treatment comparisons, will be performed as supplemental analyses.

If an FAP-related event occurs, that patient will be said to have an observed or uncensored event and will be considered a treatment failure. If a subject withdraws, that subject will be treated as a censored observation as of the last recorded clinic visit (endoscopic disease assessment).

If a subject has not progressed or is not known to have died at the date of analysis cut-off, time to first FAP-related event will be censored at the date of the last adequate endoscopy procedures before the cut-off date. Similarly, if a subject discontinues study participation due to toxicity and begins receiving other therapy, the time to FAP event will be censored at the date of the last adequate endoscopy procedure.

Prior to the primary analysis, balance will be assessed between the three arms in terms of key potential confounders measured at the baseline visit. If any of these variables is found significantly out of balance across the three groups using a 2 degree of freedom test of homogeneity at the 0.01 level of significance, it will be incorporated into -a sensitivity analysis using a stratified Cox model including that term in addition to the treatment arm. The primary result for the trial will be the unadjusted stratified log-rank test. The covariate-adjusted score test (adjusted stratified log-rank test) will serve only as a secondary analysis to aide in the interpretation of the primary result.

12.2. Secondary Efficacy Outcome and Analysis

Any improvement observed by the investigator during upper gastrointestinal (UGI) and lower gastrointestinal (LGI) visualization (i.e. endoscopy and colonoscopy) at the 6 and 12-month study visits will be described using the variables UGI Observed Improvement (UGIOI), and LGI

Observed Improvement (LGIOI). Each patient will have one pair of UGIOI and LGIOI outcomes (refer to the Statistical Analysis Plan for more detail).

UGIOI and LGIOI are binary outcomes derived from numerical determinations (henceforth, "investigator change scores" or more briefly, "scores") assigned by the investigator during each procedure, using a scale (–2, –1, 0, +1, +2) which corresponds, respectively, to the investigator's overall qualitative assessment of: much worse, worse, no change, improved, much improved. At the month 6 procedures the investigator scores UGI and LGI findings as changes from baseline. At the month 12 procedures, the UGI and LGI findings are scored relative to the month 6 procedures.

The UGIOI (and respectively, the LGIOI) secondary endpoint independently summarizes the corresponding 6- and 12-month investigator change scores according to whether or not there was *any positive improvement* at either month 6 (compared to baseline) or at month 12 (compared to baseline or month 6), under the condition that there be *no worsening at either timepoint* (compared to the preceding timepoint). Refer to the Statistical Analysis Plan for further details on the planned analysis.

12.3. Other Secondary Outcomes

Other secondary outcomes will include the following:

To explore how study treatment group relates to other efficacy outcomes, genotype, phenotype, disease locations and endoscopic findings, additional analyses are planned. These analyses will be performed in the ITT group, the Per Protocol Group, and other defined subgroups (see protocol Section 12.5, Populations for Analysis and the Statistical Analysis Plan) wherever possible and will all be clearly noted as such.

The UGIOI and LGIOI outcomes will be tabulated and summarized using the month 6 visit scores, alone. Similarly, the UGIOI and LGIOI outcomes will tabulated and summarized across all study visits.

As both part of the primary analysis, and further explored in these additional analyses, median time to event for each treatment group will be determined. This will be explored for each of the study populations (i.e. ITT, per protocol, and others), study disease stratum groups, and in the Disease Site subgroups (refer to the Statistical Analysis Plan for more details).

Pharmacokinetic data (plasma concentrations measured at patient visits) will be used to estimate population pharmacokinetic parameters for the CPP-1X (eflornithine), sulindac, and CPP-1X (eflornithine) + sulindac treatment groups (i.e., for each analyte for those patients on combination treatment).

The subcategories of FAP events will be explored by disease stratum groups, and by Disease Site subgroups (refer to the Statistical Analysis Plan).

The presence or absence of ODC polymorphisms, including the single nucleotide polymorphisms (SNPS) rs2302615 and rs2302616 and their relation to treatment group and outcome will be tested with the likelihood ratio test.

The excretion of 5 urinary polyamines (diacetylspermine, n1-acetylspermidine, n8-acetylspermidine, decarboxylated SAM, and putrescine) will be assessed in relation to treatment group and outcome, using the single point concentration data gathered from the urine samples harvested at each study visit.

Patient reported health related quality of life measures will be evaluated using HRQoL (refer to Statistical Analysis Plan for more details).

Tissue and dietary polyamine levels, as collected at patient study visits will be analyzed together with the results of the dietary questionnaires and related to treatment group and study outcomes.

Safety outcome data and analyses are described in detail in the Statistical Analysis Plan.

12.4. Sample Size Determination

The primary endpoint of this trial, time to meaningful clinical events in an orphan disease population, is novel and to date there are no published trials to draw upon that have incorporated the exact FAP-related endpoint of this trial. Available data from primary literature sources include clinical studies where polyps were counted over a fixed time period, in different FAP populations (see Appendix E for tabulated listing).

From these data a reasonable range of event frequencies was estimated to produce the sample size and power calculations incorporated into this trial. These time-to-event estimates were reviewed by key FAP opinion leaders prior to finalization of the study design. The following reflects the possible range of FAP events it was thought plausible to observe.

12.4.1. Power Calculation Assumptions

1) The level of statistical significance is set at 0.05, using a 2-sided stratified log-rank test for time-to-first FAP-related event in continuous time, for each of the two between-group comparisons (i.e. single agent sulindac vs. CPP-1X plus sulindac and single agent CPP-1X vs. CPP-1X plus sulindac). The only covariates in the log-rank test will be the treatment groups;
2) A doubling of the two-year event-free proportion from either of the single agent treatment arms to the combination treatment group;
3) Power of at least 85% to detect the above-mentioned treatment effect comparing either of the two single treatment arms to the combination arm;
4) The two single-agent treatment groups have approximately the same event rate.

The following calculations are based on our review of limited single-agent data for eflornithine and sulindac, where FAP clinical trial primary endpoints involved polyp counting. Extrapolating these data to two-year event-free proportions implies a single overall two-year event-free proportion of at least 60% to 70% for the combination treatment group and 30% in each single agent treatment group.

12.4.2. Hazard Rates

Because the power of time-to-event analyses depends on the total number of observed primary endpoints (“events”) and the hazard ratio in a given two-arm comparison of a single-agent versus combination therapy, we translate the above doubling of two-year event-free proportions into hazard ratios under a simplifying assumption of exponentially distributed time-to-event.

Furthermore, the stratified log-rank test is an optimal test (locally most powerful) under the assumption that the *ratio* of the two groups’ hazard functions remains constant over time (the proportional hazards assumption). Note that the much stronger assumption, that the individual hazard functions themselves remain constant over time, would be dubious in this trial. Therefore, irrespective of how the two-year event-free proportions are translated into hazard ratios, it is the latter which forms the *design alternative parameter* for the trial.

Under the exponential assumption, the hazard ratio (HR) comparing one treatment arm to

another is given by the natural logarithm of the two-year event-free proportion for the first arm divided by the natural logarithm of the two-year event-free proportion for the other arm. Thus if the combination arm is assumed to have a two-year event-free proportion of 60%, which is double that of the 30% two-year event-free proportions assumed for the single-agent arms, the HR is {log(0.60) / log(0.30)} = 0.4243. *This is the design alternative hazard ratio for this trial* as it represents the minimum clinically meaningful treatment effect desired for the combination therapy compared to either single-agent therapy. Insofar as the combination therapy may have a two-year event-free proportion of *at least* 60%, and may prove to be perhaps 70% or greater, the design alternative HR of 0.4243 is conservative; the true (albeit unknown) HR is thought possibly to range from 0.4243 down to 0.30 = {log(0.70) / log(0.30)}.

Given that the primary hypotheses are stated in terms of comparing either single-agent arm to the combination arm, we note that the equivalent design alternative hazard ratio becomes {log(0.30) / log(0.60)} = 1/0.4243 = 2.357.

For the anticipated range of hazard ratios, 25 to 49 events would be needed for each two-group comparison at the 2-sided 0.05 level to achieve 85% power[87,88] Assuming two-year event proportions of 70% in either of the two single-agent groups and 30% to 40% in the combination arm with 50 patients per arm, the expected number of patients with an FAP-related event in either of the two single-agent groups would be 35 and 15 - 20 in the combination arm. The study design expectation is to have 50 - 55 patients with a FAP-related event in each two arm comparison, achieving at least 85% power under the design alternative. The standard deviation around the expectation of 55 events is 4.74, so observing the required number of 49 events or more would be highly likely (the probability is about 91%). If the total number of events in either comparison were only 43, there will still be 80% power to declare a significant treatment difference under the design alternative of 0.4243.

As the two-year event proportion in the combination arm decreases from 40% with a corresponding decrease in the hazard ratio, the likelihood of observing the required number of events to maintain 85% power actually increases. For example, at the lower expectation of 50 events arising from an assumed two-year event proportion of 30% in the combination arm, the standard deviation of the total number of events in a two-arm comparison decreases to 4.58 and the probability that the observed number of events will exceed the 25 required to achieve 85% at a HR of 0.30 is virtually certain.

12.5. Populations for Analysis

12.5.1. Intent-to-Treat (ITT) Population

The intent-to-treat population includes all patients that have been randomized to one of the three study arms (CPP-1X plus sulindac, CPP-1X placebo plus sulindac, CPP-1X plus sulindac placebo). Patients will be analyzed in the group to which they were randomized, whether or not they received any treatment or completed their treatment and follow-up.

12.5.2. Safety Population

The safety population is defined as all ITT patients who received at least one dose of study medication. Patients who do not receive any study treatment (CPP-1X or sulindac or their combination) are excluded from this population. Patients will be analyzed in the treatment group for which actual treatment was initially received.

12.5.3. Per Protocol Population

The per-protocol population is defined as the subset of the ITT population that fulfill all protocol eligibility, intervention, and outcome assessments.

12.5.4. Other Populations

Within the entire study patient population there will be subsets who did not receive the full course of per protocol treatment. The major indicators for premature withdrawal are delineated below. The patient diary and pill count will define the extent of treatment compliance during the study.

For exploratory and sensitivity analyses the following subsets will be included in secondary analyses:

- Subject withdrawn for personal reasons
- Treatment discontinued because of disease symptoms
- Treatment discontinued because of patient symptoms
- Compliance <80% treatments taken
- Treatment discontinued because of intercurrent medical or surgical illness.

12.6. Other Statistical Methods

12.6.1. Demographic and Baseline Characteristics

Patients in the three populations (ITT, Safety, Per Protocol) will be summarized for demographic and baseline characteristics in a descriptive fashion. Namely, categorical and continuous-valued data will be displayed using standard summary statistics (e.g., frequency tables, n, means, medians, standard deviations, and ranges). Data will be presented per group and overall.

Demographic features summarized will include age, gender, race, institution at which each patient registered, and country among other features. Baseline characteristics will include laboratory values and disease-related characteristics, as well as any other relevant values. Categorical data will be compared among groups using chi-squared methods, while continuous-valued data will be compared using standard nonparametric methods (e.g., the Kruskal-Wallis test).[89] Significance will be defined at the 0.05 level, unless otherwise noted. Thus p-values less than or equal to 0.05 will be declared significant.

12.6.2. Patient Disposition and Treatment Summaries

Subjects will be assigned for analysis to the treatment group to which they were randomized, regardless of whether the patients received any treatment.

Subject disposition and treatment will be summarized for ITT and safety populations defined previously. Subject disposition will be consistent with the CONSORT criteria,[90] and will include per treatment group enumeration of all patients randomized, the number deemed ineligible, the number of FAP-related events, and the number of study drop outs. These will be further described in subgroups such as drop outs due to adverse events, serious adverse events, administrative withdrawals for non-compliance, withdrawals of consent for continued follow-up, withdrawals for other reasons, and the number lost to follow-up. Additional summaries will include reasons for patients discontinuing treatment and/or modifying treatment dosages. A listing of screened and ineligible patients along with the reason for each also will be summarized.

12.6.3. Categorical or Continuous-Valued Secondary Outcome and Safety Data

For categorical data, comparisons will be made between treatment groups using standard chi-square techniques as the primary approach. In particular, Cochran-Mantel Haenszel one degree of freedom test will be used to reflect the stratified randomization. Exact p-values and 95% confidence intervals by the point probability method will be reported[91].

For continuous endpoints, standard analysis of covariance (ANCOVA) methods will be used as the primary approach to compare treatment groups at end of treatment with the following covariates: baseline value, binary indicator variables for the two highest-risk stratification levels used in the randomization (using the lowest-risk, i.e., rectum/pouch polyposis, group as the reference stratum), and a binary treatment indicator (1=combination treatment, 0=single treatment).

For ordered categorical data, a Kruskal-Wallis nonparametric test for ordered categorical response will be used to compare treatment groups.[89]

Treatment-emergent adverse events will be enumerated and analyzed according to the incidence, intensity, type of adverse events, and clinically significant changes in the patient's physical examination findings, vital signs and clinical laboratory results. Safety variables will be tabulated and presented for all patients in the safety and per-protocol populations as defined previously.

Adverse events will be graded and coded using the NCI Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03). Treatment-emergent events will be tabulated, where treatment-emergent is defined as any adverse event that occurs after administration of the first dose of study drug and through 30 days after the last dose of study drug, or any event that is present at baseline and continues after the first dose of study treatment but worsens in intensity. Events that are considered related to treatment (possibly, probably or definitely drug-related) also will be tabulated separately. Tables that enumerate adverse events by severity will also be provided. Deaths, serious adverse events and events resulting in study discontinuation will be tabulated in data listings including additional relevant information on each patient. Tables will be presented both overall (all arms combined), by each treatment group separately, and by cell. Where appropriate, statistical comparisons between treatment arms will be provided using the above-mentioned methods for analysis of categorical data.

12.6.4. Subgroup Analyses

Subgroups will be analyzed in the spirit of exploratory analyses including but not limited to the various study populations and separately within each disease-prognosis stratum.

12.6.5. Health Related Quality of Life (HRQoL)

For this study four (4) instruments to measure HRQoL and patient preferences or utilities will be administered to subjects at baseline and months 3, 6, 12, 18, 24, 30 36, 42 and 48/end of treatment. These instruments include the EORTC QLQ-C30, EORTC QLQ-CR29, EQ-5D, and a modified Cancer Worry Scale.

The validity and reliability of both the QLQ-C30 and the QLQ-CR29 questionnaires have been studied by the EORTC Study Group on Quality of Life and both instruments will be scored according to the EORTC Scoring Manual and analyzed accordingly. For each single item or multi-item sub-scale, a linear transformation will be applied to standardize raw scores to range between 0 and 100. HRQoL secondary endpoints will include all single item or multi-item sub-scales from both the EORTC QLQ-C30 and QLQ-CR29 and patients will be considered as

deteriorated (or improved) for a given single item or multi-item sub-scale if their change score from baseline was 10 points or more on the standardized scale.

Patient preferences (or utilities) will also be assessed using the EuroQoL EQ-5D. Preference weights among the treatment arms will be determined using the EuroQol EQ-5D assessment of individual health states.[72,73] Quality-adjusted survival among the three treatment arms will be generated by multiplying the utility value by the amount of time spent in a specified health state.

The modified version of the Cancer Worry Scale will also be administered and it will be scored according to the guidance provided by Lerman *et al*[74].

HRQoL data will be obtained while patients are receiving treatment. At the time of an FAP-related event (primary outcome), additional long-term clinical follow-up and QoL data will not be obtained as part of this trial. Hence, HRQoL trends comparing the nine subsets will be obtained, but comparative longitudinal analyses defining the impact of an FAP-related event on QoL will not be feasible until subsequent long-term studies are performed.

12.6.6. Dietary Assessment

The FFQ was developed by the Nutrition Assessment Shared Resource (NASR) of the Fred Hutchinson Cancer Research Center. NASR periodically updates its standard FFQ to reflect U.S. food consumption patterns and major changes in the market place.[82,83] Data from the FFQ will be analyzed using a polyamine database[69] and will calculate the average daily levels of putrescine, spermidine, and spermine in the diet. Dietary assessments via the FFQ will be obtained at baseline, months 12, 24, 36, 42 (only if end of treatment) and 48/end of treatment for subjects at North American (U.S. and Canada) sites only.

12.7. General Procedures for Handling of Missing Data

Every reasonable effort will be made to continue follow-up of all study participants, including those who discontinue randomized therapy, to prevent data loss. It is recognized that missing values represent a potential source of bias in a clinical trial and so every effort will be undertaken to fulfill all the requirements of the protocol concerning the collection and management of data.

For the primary time to event analysis, the only possible patient outcome is an observed FAP-related event, or a censored observation. Participants who are lost to follow-up for reasons deemed unrelated to their health status will be censored at the time their status is last known, based upon data collected at the last recorded clinic visit. For patients who may have missed a study visit, every effort will be made to obtain endoscopic results at their close-out visit and those endoscopy results will be used for the primary analysis.

Secondary analysis data include the presence of a specific genetic mutation, and urinary metabolite concentrations (See Section 12.2). The main analysis of the secondary objectives will include collected data only, without imputing or weighting data to compensate for missing data. For sensitivity analyses involving secondary endpoints with missing data, we will use the last observation carried forward (LOCF) method to complete the missing data. Any sensitivity analysis that incorporates LOCF will be clearly noted. Sensitivity analyses of these data will be performed to explore study results more fully, in a manner consistent with ICH Guidance "*E9 Statistical Principles for Clinical Trials (February, 1998)*".

All available efficacy and safety data will be included in data listings and tabulations. Data that are potentially spurious or erroneous or appear as outliers will be examined using standard data management operating procedures, prior to database lock and statistical analysis.

12.8. Interim Monitoring and the Data Monitoring Committee

A Data Monitoring Committee (DMC) will oversee the performance and safety conduct of this study. The DMC will consist of at least three members (two MDs and one statistician as voting members) who will receive confidential reports on a periodic basis. The DMC will be responsible for decisions regarding possible termination of the study for either futility or safety reasons.

A detailed DMC Charter will be produced separately by the DMC membership. It is anticipated that any reviews of study data will be performed in a blinded manner, looking at pooled data (all treatment groups combined into one group) to assess mission-critical parameters such as overall recruitment and event rates. Any pre-specified interim analyses will be conducted in a blinded manner. Of course, patient safety issues take precedence over bias-protection and control of type I error, and so the DMC will have the privilege of breaking the blind on a need-to-know basis if safety issues of concern arise in order to consider risk-benefit issues. Details concerning DMC responsibilities and duties may be submitted as a stand-alone document to the FDA and EMA, including items such as specification of early termination rules and other matters as the DMC deems to be important and relevant to the ethical conduct of this study.

CPP will inform the DMC that there will be two study evaluations for the DMC to consider during the trial, one interim look for sample size reassessment and one look for futility.

The method for reassessment of sample size is based upon the FDA Guidance, *"Adaptive Design Clinical Trials for Drugs and Biologics (February 2010)*". There will be no hypothesis testing. The DMC will assess the observed trial event rate based on pooled data only. They will make a recommendation to the Sponsor on whether the pooled event rate is sufficient to preserve the integrity of the trial, and if not, to recommend a revised sample size. For this assessment the study statistician will, if possible, estimate the overall observed event rate and 90% confidence interval. This assessment will be performed using data from a single time point, when enrollment is approximately 95% complete. If this type of assessment is not possible, then as assessment will be performed taking into consideration the total number of subjects randomized, total number of events, total number of dropouts, and cumulative study safety data.

Prespecified Interim Efficacy and Futility Analysis

A pre-specified interim efficacy and futility analysis will be conducted in a blinded manner. The assessment will be performed after a total of 45 primary endpoints have occurred, which represents 50% of expected maximum trial information, or as soon thereafter as possible. Refer to the Statistical Analysis Plan for more details.

The analysis will be performed for each of the two treatment comparisons contained in the primary objective:

1. CPP-1X placebo + sulindac active vs. CPP-1X active + sulindac active,

   and

2. CPP-1X active + sulindac placebo vs. CPP-1X active + sulindac active

The efficacy analysis will use a modified Haybittle-Peto stopping rule based on the stratified log-rank *Z*-score. If that *Z*-score equals or exceeds 3.2905 in absolute value, for either two-arm comparison, the difference between treatment arms would be declared statistically significant at the two-tailed 0.001 level of significance. In that case it may be reasonable for the DMC to initiate a conversation about stopping the trial on ethical grounds. Assuming this is not the case

and the trial continues to its planned end, the *Z*-score criterion for declaring significance at the 5% level at the end of the trial will be increased in magnitude to plus or minus 1.962 in order to preserve the overall type I error rate for the trial at 0.05.

For the futility analysis, the DMC will be provided with the numerical value of the stratified log-rank *Z*-score. The futility analysis uses a one-sided futility stopping criterion of $Z = -0.50$. That is, if the *Z*-score is less than or equal to −0.50, an investigation will be initiated to consider stopping the trial for futility or discontinuing one of the single-agent treatment arms. The futility stopping criterion of $Z = -0.50$ is consistent with a conditional power of less than 20%. That is, assuming between 44 and 60 FAP-related events have occurred by trial end in either of the two-arm comparisons (where between 52 and 55 are expected), if the log-rank critical ratio *Z*-score were equal to −0.5 (or less) when one-half the expected total number of events had been observed (namely, 45 across all three arms), then under the design alternative hazard ratio of 2.3569, there would be no more than a 20% chance of declaring a significant benefit of the combination therapy compared to the single agent therapy if the trial were to continue to the planned end. In that case, it would be reasonable for the DMC to consider stopping or altering the trial on grounds of futility. The DMC will also be provided with the conditional power of the observed *Z*-score for each two-arm comparison.

Any numerical values generated from the futility analysis (such as *Z*-score, conditional power, etc.) must be treated as confidential by the DMC and Independent Statistician at the CRO. If the DMC recommendation is to continue the study as planned, such numerical values will not be forwarded or conveyed in any manner to the Steering Committee, Sponsor, or any other parties.

12.9. Pharmacokinetic Analysis for Eflornithine and Sulindac

The text that follows applies to each of the two compounds, eflornithine and sulindac. Separate analyses will be performed for each drug.

To perform the population pharmacokinetic analysis, a dataset will be constructed as follows:

1. All subjects with at least one sample will be included in the analysis. Actual sample time will be used in the analysis.
2. Dosing history will be assembled based on CRF data. Dosing records will assume 100% compliance, except as documented in the CRF.
3. The dataset will be constructed using a script in R (www.R-project.org). All steps will be documented. All decisions regarding handling of aberrant data will be documented.
4. Covariate data (age, extent of prior colectomy, body size, gender, race, laboratory values, *etc.*) will be included in the dataset. The dataset will be constructed using values obtained temporal to the time of sampling.

The pharmacokinetic analysis will be performed using NONMEM (version 7.1 or greater). Graphics will be created using PLT Tools (version 3.0 or greater) using R (version 2.11 or greater). Initially, linear compartmental models will be applied to the data. The choice between 1-, 2-, and 3-compartment models will be based on the graphics and the minimum value of the objective function. If graphics suggest nonlinearity in pharmacokinetics with respect to dose and/or concentration, nonlinear models will be evaluated.

Once the optimal structural and error model has been determined, covariate effects will be assessed using a variety of tools including graphics of post hoc parameter estimates vs. covariates, a general linear model of parameters as a function of covariates, or an automated

covariate search (PLT Tools). Covariates will be incorporated into the model if they are physiologically appropriate, achieve statistical significance (generally requiring a P value < 0.01 in this exploratory environment), and improve the graphics.

Once a final model is determined, the model will undergo validation. The strength of covariate effects will be determined using likelihood profiles. Confidence intervals for parameter estimates will be determined using bootstrap techniques. If appropriate, a visual predictive check will be performed.

All NONMEM outputs and graphics will be provided with the population pharmacokinetic report. Results will be summarized detailing the process of model building. The report will include key graphics demonstrating the fit of the model to the data and covariate effects.

13. STUDY MANAGEMENT AND REPORTING PROCEDURES

13.1. Data Monitoring

A Data Monitoring Committee (DMC) will oversee the performance and safety conduct. The DMC will consist of at least three members (two MDs and one statistician as voting members) who will receive confidential reports on a periodic basis. The DMC will be responsible for decisions regarding possible termination of the study for either futility or safety reasons, refer to Section 11, Assessment of Safety and Section 12.8, Interim Monitoring and the Data Monitoring Committee.

13.2. Patient Tablet Dispensing Record

Three (3) month supplies of study drug(s) are issued in person or by special arrangement. Subjects will keep a written diary concerning their compliance in taking the four tablets daily. The drugs are to be taken at approximately the same time each day with food, preferably in the morning. If the dose is missed, the tablets may be taken with mid-day or evening meals. If an entire day is missed, this should be indicated in the weekly dose accountability in the medication diary, but double-dosing the following day is not allowed. If the subject vomits within an hour after taking the tablets, the subject will record a missed dose in the diary. If the subject vomits more than 1 hour after taking the tablets, no dose was missed. In either case, no additional tablets are to be taken until the scheduled dose the next day. Any unused medication must be returned at the subject's next scheduled visit and an accounting of the medication will be performed and recorded by the research nurse or other qualified individual.

13.3. Investigator Documentation

The Investigator will provide the Sponsor with a fully executed FDA form 1572 including the Investigator's dated curriculum vitae. A current curriculum vitae is also required for each sub-Investigator listed on the FDA Form 1572. A current dated curriculum vitae is defined as updated within 2 years.

The Investigator will indicate on the FDA Form 1572 the name and location of the clinical laboratory which will be used for subject evaluation. The laboratory's certification, certification number and date of certification and the laboratory normal values will be provided. Any changes in the clinical laboratory or laboratory values will be provided promptly to the Sponsor who will report it to the FDA.

The Investigators and Sub-Investigators must provide CPP with an FDA Form 3454 certifying the absence of financial interests and arrangements, or Form 3455 disclosing such financial interests and arrangements and any steps taken to minimize bias.

13.4. Protocol Amendments

All amendments to the study protocol must be submitted to the IRB/IEC/REB for written approval. The approval letter, signed by the IRB/IEC/REB Chairperson, must refer specifically to the Investigator, the protocol number and protocol title, the protocol amendment number and the date of the protocol amendment. A copy of the approval letter and revised informed consent document (if appropriate) must be sent to CPP. A protocol amendment may be implemented only after it has been approved by the IRB/IEC/REB and submitted to the FDA and other regulatory agencies as appropriate. In the case of a protocol change intended to eliminate an apparent immediate hazard to subjects, the change may be implemented immediately, but the change must then be documented in a protocol amendment and approved as described above.

13.5. Access to Source Data and Documents

Monitors and/or auditors of CPP or representatives of the Sponsor must be allowed to visit and monitor all study site locations periodically to assess the data, quality and study integrity. The monitors and/or auditors will review study records (typically CRFs) and directly compare them with the source documents and discuss the conduct of the study with the Investigator and verify that the investigational site is compliant and continues to be acceptable. In addition, the site may be audited by government inspectors who must be allowed access to CRFs, source documents and other study files. The site must promptly notify CPP of any inspections scheduled by regulatory authorities, and also forward copies of the inspection reports to CPP.

13.6. Investigational Agent Records and Accountability

It is the Investigator's responsibility to ensure that accountability records of drug use and disposition are maintained at the study site and that the drug is maintained in a secure location under storage conditions prescribed by the Sponsor. The site pharmacist or appointed investigational agent monitor will be the individual completing the records or logs for accountability and drug dispensing at each site. The site pharmacist must comply with all applicable regulations and guidelines. The logs should include the amount of drug received; amount currently on site, drug lot or batch numbers; amount dispensed to each study subject with appropriate subject study identification numbers; non-study disposition (wastage, broken), amount returned to site and Sponsor, amount destroyed at study if requested. CPP will provide forms to assist with drug inventory if the site does not have an established procedure that meets the requirements. Drug inventory records will be inspected by the Sponsor's study monitors during the period of study treatment. Audits will be done to verify drug accountability. If a site has been determined to be non-compliant with drug accountability corrective action will be initiated.

At the completion or termination of the study, all unused investigational agent will be returned to the repository unless authorized in writing to be destroyed at the site. If the drug is to be destroyed on site, appropriate policies and procedures at the site must be in place for proper disposal of chemotherapeutic agents. These procedures will be reviewed by Sponsor's study monitors prior to providing written authorization for on-site drug destruction. The unused study drug can only be destroyed after being inspected and reconciled by the Sponsor's study monitor.

13.7. Data Handling and Record Retention

Following the completion and closure of the clinical study, in accordance with applicable regulatory requirements, the Investigator will maintain a copy of all study records in a safe and secure location. Completed original CRFs, which are dated and signed by the investigator, and any resolved query reports will be retained by the Sponsor. A copy of each completed CRF and signed resolved query report must be retained at the investigational site. The Investigator will retain a copy of all study records in a secure location for a minimum period of 2 years after licensure for marketing of drug or 15 years from the close of the trial or until receipt of notification by Sponsor that clinical development of this treatment has been terminated.

13.8. Protocol Deviations

The Investigator is not permitted to alter or deviate from the protocol without a written waiver from the Sponsor. This waiver should also be reported by the Investigator to his/her IRB/IEC/REB. An immediate and unapproved deviation is permitted if immediate subject safety concerns mandate a deviation.

13.9. Study Termination

The Sponsor may terminate the study at any time. If the study is terminated, the Sponsor will promptly notify the Investigator to enter no further subjects on the study and remove current subjects from the study. The Sponsor will also inform regulatory authorities of the action.

1. The study will also be terminated when the objectives have been fully met and all of the designated data collected.
2. The Sponsor reserves the right to terminate an Investigator's participation in this clinical trial for refusal of the Investigator and/or site to comply with any requirements stated in this clinical protocol.

13.10. Use of Data and Publication

All data and results and intellectual property rights in the data and results that are derived from the study will be property of CPP. CPP may utilize the results and data in variety of ways including submission to regulatory authorities or to other investigators under disclosure. Data from any individual center must not be published or presented until the complete multicenter study has been published or presented in full. Subsequently, an investigator may use the data derived from the clinical study for scientific purposes but must discuss any publication with the Sponsor prior to submission or release of any data. The Sponsor is aware of the rights of an Investigator to publish the results when the study is completed, and the Investigator must provide a draft of the abstract or manuscript to the Sponsor within 30 to 60 days prior to submission of the abstract or manuscript. The Sponsor will provide a timely review and response to the Investigator. In the event of a difference of opinion between the Investigator and Sponsor, all efforts will be put forth to find a solution that is agreeable to both the Sponsor and Investigator. However, the final decision for submission/dissemination of results rests solely with the Investigator.

14. HUMAN SUBJECTS

The study will not be initiated until a protocol has been filed to the IND or approved by the appropriate regulatory authorities and the informed consent documents have been fully reviewed and approved by each participating institution's IRB/IEC/REB. The approval and associated documents will be provided to the Sponsor. All relevant regulations of the regulatory authorities will be followed.

14.1. Ethical Conduct

The study will be conducted in compliance with the regulations from the FDA, Health Canada, local competent authorities, and the EMA, including Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), Good Clinical Practice guidelines (ICH), and Obligations of Clinical Investigators (21 CFR 312), Food and Drug Regulations (C.R.C., C.870), C.05.001 - Division 5, Drugs For Clinical Trials Involving Human Subjects, Regulation (EU) No.1235/2010, Directive 2010/84/EU, Directive 2001/20/EC (The Clinical Trials Directive), Commission Directive 2005/28/EC (The GCP Directive), and any other applicable country specific regulations.

The protocol will be reviewed and approved by each institution's IRB/IEC/REB, and as applicable, any country or regional IRB/IEC/REB. Written documentation of the IRB/IEC/REB approval of the protocol and informed consent must be provided by the Investigator to the Sponsor prior to study initiation. Serious adverse events regardless of causality will be reported to the Sponsor and to the IRB/IEC/REB, and the Investigator will keep the IRB/IEC/REB informed as to the progress of the study.

14.2. Informed Consent

The Investigator or his designee will explain the nature of the study and will inform the subject that participation is voluntary and that they can withdraw at any time. Written informed consent and required authorization to use private information will be obtained and documented from each subject prior to entry into the study.

The consent form generated by the Investigator must be approved by the IRB/IEC/REB and be acceptable to Cancer Prevention Pharmaceuticals. Each subject's signed informed consent form must be kept on file by the Investigator for possible inspection by regulatory authorities and or Cancer Prevention Pharmaceuticals personnel or representatives of Cancer Prevention Pharmaceuticals.

14.3. Confidentiality

The Investigator and his staff shall maintain the confidentiality of all subject records. Subject data will be made available upon request to monitors from CPP Corporation (study Sponsor), regulatory authorities, the Institutional Review Board, Independent Ethics Committee, or Research Ethics Board, and to other government agencies that have responsibility for clinical research activities.

Data that is released by the Investigator to the Sponsor, regulatory authorities, or the IRB/IEC/REB will not be directly traceable to the subject. In the event that a publication of this research incorporates a subject's medical data, the data will not identify the subject.

15. LISTING OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse event
ALT	Alanine Amino Transferase
a.m.	Morning
APC	Adenomatous Polyposis Coli-tumor suppressor gene
AST	Aspartate Amino Transferase
BID	Twice a day
^{0}C	Degrees centigrade
CBC	Complete blood cell count
CFR	Code Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
cm	Centimeters
COX	Cyclooxygenase
CPP	Cancer Prevention Pharmaceuticals
CPP-1X	Eflornithine, DFMO, difluoromethylorthine
CRC	colorectal cancer
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
dB	Decibels
DFMO	Eflornithine, CPP-1X, difluoromethylorthine
dL	deciliter
DMC	Data Monitoring Committee
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic Acid
EDTA	Ethylene Diamine Tetra Acetic Acid
EFS	Event free survival
EKG	Electrocardiogram
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of Treatment
EU	Europe
FAP	Familial Adenomatous polyposis
FDA	Food and Drug Administration
FFQ	Food Frequency Questionnaire
GCP	Good Clinical Practices
GI	Gastrointestinal
HCG	Human Chorionic Gonadotropin
HDPE	High density polyethlylene
HEENT	Head, Ear, Eyes, Nose, Throat
HGD	High grade dysplasia
HRQoL	Health-Related Quality of Life
IB	Investigator's Brochure
ICH	International Committee on Harmonization
IME	Important medical event

Abbreviation	Description
IND	Investigational New Drug Application
InSiGHT	International Society for Gastrointestinal Hereditary Tumours
IRA	Ileal-rectal anastomosis
IRB/IEC/REB	Institutional Review Board/Independent Ethics Committee/Research Ethics Board
ITT	Intent-to treat
IUD, IUS	Intrauterine device, Intrauterine system
LGI	Lower gastrointestinal
LGIOI	LGI Observed Improvement
LOCF	Last observation carried forward
mg	milligrams
mL	milliliters
mm	millimeters
MST	Mountain Standard Time
N	Normal
NCBI	National Center for Biotechnology information
NCI	National Cancer Institute
NSAIDS	Nonsteroidal anti-inflammatory drugs
NASR	Nutrition Assessment Shared Resource
ODC	Ornithine decarboxylase
OMIM	Online Mendelian Inheritance in Man
PCR	Polymerase Chain Reaction
PK	Pharmacokinetics
PO	By mouth, orally
PSA	Prostate specific antigen
QLQ	Quality of Life Questionnaire
QoL	Quality of Life
RNA	Ribonucleic acid
RSI	Reference Safety Information
RX	Treatment
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SNP	Single nucleotide polymorphism
Spd:Spm	Spermidine to spermine ratio
SWOG	Southwest Oncology Group
TEN	Toxic epidermal necrosis
UGI	Upper gastrointestinal
UGIOI	UGI Observed Improvement
ULN	Upper limit of normal
US	United States
$T_{1/2}$	Half-life
WBC	White Blood Cell
WHO	World Health Organization

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APPENDIX A SPIGELMAN'S SCORE AND STAGE_ENREF_92

Modified Spigelman's Score and Classification (Saurin, 2004)[92]

	Score		
Factor	**1 Point**	**2 Points**	**3 Points**
No. of polyps	1-4	5-20	> 20
Polyp size, mm	1-4	5-10	> 10
Histology	Tubulous	Tubulovillous	Villous
Dysplasia	Low grade	—	High grade*

NOTE: Classification as follows based on score scale.

Stage 0: no polyps

Stage 1: 1 to 4 points

Stage 2: 5 to 6 points

Stage 3: 7 to 8 points

Stage 4: 9 to 12 points

*High-grade dysplasia would be assigned to any epithelium showing nuclear stratification all the way to the tops of the cells and loss of mucin production. It can encompass intraepithelial carcinoma if the cells are pleomorphic or even cribiformed in architecture but still all located above the basement membrane.

Comment: All adenomas in the duodenum demonstrate at least low grade dysplasia; if intermediate grade use low grade for points.

Vienna Classification of Gastrointestinal Epithelial Neoplasia (Schlemper *et al.*, 2000)[93]

Category 1	Negative for neoplasia/dysplasia
Category 2	Indefinite for neoplasia/dysplasia
Category 3	Non-invasive low grade neoplasia (low grade adenoma/dysplasia)
Category 4	Non-invasive high grade neoplasia 4.1 High grade adenoma/dysplasia 4.2 Non-invasive carcinoma (carcinoma in situ)[a] 4.3 Suspicion of invasive carcinoma
Category 5	Invasive neoplasia 5.1 Intramucosal carcinoma[b] 5.2 Submucosal carcinoma or beyond

[a] Non-invasive indicated absence of evident invasion.

[b] Intramucosal indicated invasion into the lamina propria or muscularis mucosae.

APPENDIX B InSiGHT RECTUM/POUCH ASSESSMENT AND STAGE[94]

_ENREF_95

Stage	Polyp Description	Recommended Intervention	Comment
0	0-10 polyps, all <5mm	Repeat FS in 1 years	
1	10-25 polyps most <5mm, none >1cm	Ablate polyps; repeat sigmoidoscopy in 1 year	Chemopreventive may be considered
2	10-25 polyps, any >1cm, amenable to complete removal	Repeat sigmoidoscopy 6 months Polypectomy preferred	Removal of large polyps clearly necessary Chemopreventive valuable
3	> 25 polyps amenable to complete removal, or any incompletely removed sessile polyp, or any prior evidence of HGD, even if completely excised	Repeat sigmoidoscopy 3-6 months; consider proctectomy	Large polyps must be removed; second opinion on polyp management helpful
4	>25 polyps not amenable to complete removal, or any incompletely excised sessile polyp showing HGD; any invasive cancer	Proctectomy/pouch revision +/- ileostomy clearly indicated within 3 months	Any decision to delay surgery must be highly individualized and based on compelling circumstances

Patients who cannot be allotted a particular stage (e.g., patients with mix polyposis) contact Cancer Prevention Pharmaceuticals for assistance with staging assignment.

APPENDIX C NEW YORK HEART ASSOCIATION CLASSIFICATION TABLE

NYHA Classification - The Stages of Heart Failure

In order to determine the best course of therapy, physicians often assess the stage of heart failure according to the New York Heart Association (NYHA) functional classification system. This system relates symptoms to everyday activities and the patient's quality of life.

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

APPENDIX D Desmoid Staging System[9]

Stage	Description
I	Asymptomatic, <10 cm maximum diameter, and not growing*
II	Mildly symptomatic, <10 cm maximum diameter, and not growing
III	Moderately symptomatic or bowel/ureteric obstruction, or 10 to 20 cm, or slowly growing
IV	Severely symptomatic, or >20 cm, or rapidly growing

Mildly symptomatic = sensation of mass, pain, but no restrictions;
Moderately symptomatic = sensation of mass, pain; restrictive but not hospitalized;
Severely symptomatic = sensation of mass, pain; restrictive and hospitalized.
* Stage I may also include larger, stable, asymptomatic desmoids

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APPENDIX E Event Rate Summary Table

Familial Adenomatous Polyposis (FAP) Review: Evidence-Based Projected Event Rates at 2 Years

Rectum (after IRA) and Pouch (after Ileal-Pouch Anal Reconstruction)		
Key References	**Comments**	**Event/Rate**
Bertagnolli, et al., N Eng J Med, 2006 Bulow, et al., Dis Colon Rectum, 2008 Church, et al., Surg Onc Clin N Am, 2009 Church, et al., Dis colon Rectum, 2005 Groves, et al., Dis Colon Rectum, 2005 Huang, et al., Church, Familial Cancer, 2011 Nieuwenhuis, et al., Dis Colon Rectum, 2009 Tonelli, et al., J Surg Onc, 2000 Vasen, The Lancet, 1996 West, et al., Gut, 2010	• 80% of patients develop adenomas within the pouch body. • 71% ↓of adenomas after 4-6 mo. Sulindac (300-400mg/day)-analysis combined randomized studies. • Incidence of pouch adenomas is time-dependent with 42% of patients at 7 yrs from pouch construction. • Median time from pouch construction to diagnosis pouch adenomas, 4.7 yrs (0.5-12 yrs). • Celecoxib treated patients, median time to first polypectomy post IRA was 18.69 months; 90.9% (30 patients) had a post IRA rectal polypectomy. • Celecoxib treated patients, post IPAA, 3 of 24 pts (12.5%) had post IPAA polypectomy, 21 censored. 25th and 50th percentiles of time to first polypectomy in IPAA patients was 169.9 months	• 80% of patients develop adenomas within the pouch body. • Celecoxib treated patients, median time to first polypectomy post IRA was 18.69 months; 90.9% (30 patients) had a post IRA rectal polypectomy. **Summary Projected 2 year Event Rate: Excisional intervention and/or high risk adenoma – 40-60%**
Duodenal Disease		
Key References	**Comments**	**Event/Rate**
• Recurrence rate of adenoma development is ≥ 50% after endoscopic treatment and treatment is associated with 17% complication rate (perforation, hemorrhage, pancreatitis) • Rate of progression between Spigelman stages variable, 4 – 11 yrs	• 95-100% of all FAP patients develop duodenal adenomas • 10-25% of patients have Stage III/IV • 36% of Spigelman Stg IV develop cancer • Endoscopic resection/ablation - local recurrence rate 72.5% with mean follow-up interval of 12.8 months. Surgical resection-30% mean follow-up of 44 months, Definitive resection 47 pts with recurrence rate of 9%. Surgical morbidity-48%. • Patients down staged from Spigelman stage IV demonstrate increased rate of disease progression back to severe disease.	**Summary Projected 2 Year Event Rate: Excisional intervention, cancer – 50%**
Pre-Colectomy		
	Comments	**Event/Rate**
	• Diagnosis with recommendation to proceed with prophylactic colectomy or proctocolectomy.	**Summary Projected 2 Year Event Rate: Excisional intervention, cancer – 90%**