

# Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Burke CA, Dekker E, Lynch P, et al. Eflornithine plus sulindac for prevention of progression in familial adenomatous polyposis. *N Engl J Med* 2020;383:1028-39. DOI: 10.1056/NEJMoa1916063



This supplement contains the following items:

1. Original protocol, final protocol, and summary list of all changes.
2. Original statistical analysis plan, final statistical analysis plan, and summary list of all changes.

**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)**

**Date: April 16, 2013**

**Version: 2.0**

**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

#### 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)

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)

### **1.2. Sponsor and Study Monitor**

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inVentiv Health Clinique, Inc. (formerly PharmaNet/i3) in Quebec City, Canada will perform the bioanalysis for the pharmacokinetic samples collected.

#### 1.4. Signature Authority for Protocol and Protocol Amendments

Alfred M. Cohen, M.D., F.A.C.S., F.A.S.C.R.S.  
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## 1.6. Study Schema

### SCHEMA

#### MAJOR ELIGIBILITY CRITERIA

1. Diagnosis of Familial Adenomatous Polyposis (FAP) with confirmed APC mutation AND age  $\geq 18$  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

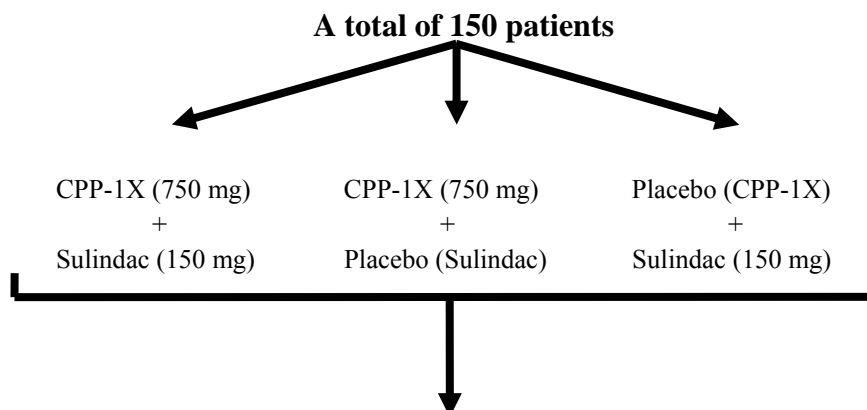
#### Stratification

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



For enrolled subjects treatment will continue for 24 months, or until occurrence of an FAP-related event as defined in the protocol. Drugs taken once daily.

## **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<sup>®</sup>, (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)<sup>1</sup> can accurately predict those with adenoma that are most likely to progress to cancer. Bulow and colleagues<sup>2</sup> 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.<sup>3-6</sup> 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.<sup>7-9</sup> Although an important site of disease and morbidity for FAP patients, this protocol will focus on intestinal polyposis only.

Vasen and colleagues<sup>10</sup> 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  $\geq 1$  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.<sup>11-15</sup> The biology of common colorectal cancer is similar to the FAP phenotype. Wallace and Lynch<sup>16</sup> 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<sup>17</sup> 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<sup>18</sup> 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 not statistically beneficial in the duodenum.

Giardello and his group<sup>19</sup> 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.*,<sup>20</sup> 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<sup>21</sup> 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<sup>22</sup> 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 recently 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.<sup>23,24</sup> 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.<sup>25,26</sup> Patients were randomized to placebo control, celecoxib 100 mg twice daily, and celecoxib 400 mg twice daily. In the Steinbach report,<sup>25</sup> 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. Dr. Patrick Lynch, the study Principal Investigator, reported results from this trial in abstract form at the 2012 Digestive Diseases Week (DDW) meeting in San Diego and the 2012 Collaborative Group of the Americas for Inherited Colorectal Cancer in Boston.<sup>27,28</sup>

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<sup>2</sup>), 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.<sup>29-31</sup>

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 2012 trial provides the first evidence of effect of eflornithine, at an average daily dose of 750 mg in patients with FAP. 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 mgs 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.<sup>32</sup> In a second study, 291 people with prior non-melanoma skin cancers were treated with eflornithine alone (500 mgs/m<sup>2</sup> 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.<sup>33</sup> 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.<sup>34</sup> 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.<sup>35</sup> 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<sup>36,37</sup> and sporadic breast cancer.<sup>38</sup> In addition, two independent groups have reported that this same polymorphism is associated with prostate cancer<sup>39</sup> and colon cancer survival.<sup>40</sup>

### **2.3. Sulindac and Eflornithine; Colorectal Polyp Chemoprevention**

Meyskens and colleagues<sup>41</sup> performed a Phase III double-blind trial involving resected sporadic adenoma patients treated 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 target of the *MYC* oncogene and *MYC* transcription is suppressed by the *APC* gene product.<sup>42,43</sup> ODC enzyme activity and polyamine contents are elevated in the apparently normal colonic mucosa of genotypic FAP patients, compared to FAP normal family members.<sup>44</sup> 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.<sup>45</sup> Studies in animal models of FAP indicate that eflornithine alone is effective in reducing the number of intestinal<sup>29</sup> and colonic<sup>30</sup> 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.<sup>46</sup> Combination treatment with eflornithine and sulindac dramatically reduce the incidence of metachronous colorectal adenomas in patients with prior sporadic adenomas.<sup>41</sup> 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.<sup>31</sup> 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<sup>2</sup>/day.<sup>47</sup> 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<sup>2</sup>/day as a dose range that effectively reduced colorectal tissue polyamine contents.<sup>35</sup> Oral doses in this range achieve serum concentrations that inhibit ornithine decarboxylase enzyme activity and polyamine synthesis in cell culture models.<sup>48</sup> 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 polyps.<sup>41</sup> Based on an average adult body surface area of 1.6 m<sup>2</sup>,<sup>49</sup> 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.<sup>41,50</sup> 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.<sup>34</sup>

Recently, a clinical trial of eflornithine in combination with another NSAID for prevention of polyps in FAP patients has been reported. Lynch *et al.*<sup>27,28</sup> have reported in abstract form only results of a trial using 500 mg/m<sup>2</sup>/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<sup>2</sup>/day eflornithine for 4-5 years.<sup>33</sup> 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.<sup>33</sup>

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.<sup>44</sup> These levels are higher than those reported for patients with sporadic risk of colorectal cancer.<sup>51</sup>

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.<sup>33</sup> The Lynch study provides evidence for efficacy of the higher eflornithine dose in FAP patients.<sup>27,28</sup>

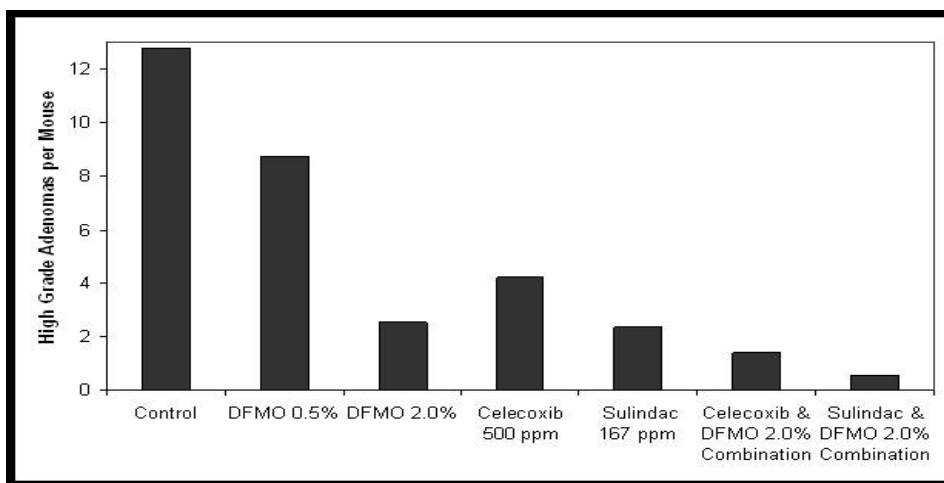
## 2.6. Rationale for Sulindac Dose

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.<sup>43</sup> 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 150 $\mu$ M for 24 hour exposure times.<sup>52</sup>

Eflornithine-sulindac combinations are potent inhibitors of intestinal carcinogenesis in mouse models,<sup>31</sup> Figure 1.

**Figure 1 - Eflornithine-Sulindac Combinations Mouse Model**



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A detailed review of the clinical pharmacokinetic of sulindac has been written<sup>53</sup> 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,<sup>54</sup> 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<sup>20,21,55,56,57,58</sup> 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.<sup>59</sup> 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.<sup>55</sup> 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<sup>60</sup> – 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<sup>61</sup> 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.<sup>61</sup> These results suggest a possible interaction between eflornithine/sulindac treatment and baseline cardiovascular risk score on cardiovascular events. Furthermore, they have implications for this FAP trial, and will affect eligibility (all patients with baseline high cardiovascular risk scores are not eligible for enrollment).

### **2.7.2. Ototoxicity Risk**

In the Meyskens eflornithine/sulindac Phase III randomized placebo-controlled colon adenoma prevention trial<sup>41</sup>, 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.<sup>34</sup>

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.<sup>41</sup> No difference in ototoxicity was observed between NSAID alone and combination eflornithine NSAID arms in the Lynch 2012 trial of FAP patients, using an eflornithine dose of 750 mgs oral daily.<sup>27,28</sup> Bailey and colleagues have recently updated their study of patients with prior non-melanoma skin cancer that were treated with 500 mg/m<sup>2</sup> (also rounded to the nearest 250 mg as they used eflornithine tablets) for 4-5 years.<sup>62</sup> The Bailey study demonstrated a significant ( $P < 0.05$ ) increase in uniformly transient audiometric (but not clinically detectable) hearing loss in participants on eflornithine.<sup>33</sup> The follow-up study did not report any clinically significant differences in hearing as compared to the placebo group.<sup>62</sup>

### **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 (Watson Laboratories, Inc.)<sup>63</sup> 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<sup>2</sup> 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.<sup>10</sup> The marginal benefit of endoscopic management of the duodenum is reviewed and tabulated (Table 4) in the paper by Brosens and colleagues.<sup>64</sup> 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 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. 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 over a 24 month treatment period in patients with Familial Adenomatous Polyposis (FAP).

## **4. INVESTIGATIONAL PLAN**

### **4.1. Study Population**

- Diagnosis of phenotypic classical FAP, age  $\geq 18$  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:
  - CPP-1X placebo with sulindac (150 mg)
  - 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 24 months.

### **4.3. Randomization**

A total of 150 eligible patients will be enrolled in this study. Patients 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 patient 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 time to the first occurrence of any FAP-related event in the patient 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, cancer or death. Section 8.2.9 provides complete detail.

#### **4.5. Secondary Outcomes**

Secondary efficacy outcomes in this study will include the following:

1. To evaluate the potentially effect modifying properties of:
  - a. Presence or absence of an ODC polymorphism
  - b. The excretion of 4 urinary polyamines (diacetylspermine, n1-acetylspermidine, n8-acetylspermidine and decarboxylated SAM)

Other secondary outcomes in this study include the following:

1. Safety outcomes will be assessed by summary analysis of adverse events and clinical laboratory abnormalities.
2. Pharmacokinetic outcomes will be assessed by evaluating the population pharmacokinetics for CPP-1X (eflornithine) and sulindac.
3. Evaluate tissue and dietary polyamine levels.
4. Patient reported quality of life will be evaluated using HRQoL and patient utilities.
5. A pilot evaluation of an FAP-specific assessment, the time to the first FAP-related beneficent event, will be studied. This will involve analyzing the endoscopic polyposis data for regression of pre-colectomy colorectal polyposis, rectal/pouch polyposis, and regression of duodenal polyposis.
6. An analysis of the components and subgroups included in the primary analysis, and their contribution to the primary outcome.

#### **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 patients 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 the scheduled colonoscopy/proctoscopy, a sample of normal rectal mucosa and a random urine sample will be obtained at baseline, 6 months and 24 months 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<sup>0</sup>C freezer. Random urine samples (15 mL minimum) will be collected and stored in a -70 – 80<sup>0</sup>C freezer.

Polyamine content: Polyamine analysis will be performed as described previously.<sup>35</sup> 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 (BCA) 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.<sup>35,65</sup>

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.<sup>66</sup>

#### **4.8. Pharmacogenetic and Genetic Analysis**

A peripheral blood sample will be collected from enrolled patients 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 oligonucleotide primers designed to amplify a 172-bp fragment containing the polymorphic base at +316 (Applied Biosystems). Allele-specific TaqMan probes will be synthesized with different 5' labels (6-carboxyfluorescein or VIC) and the same 3' quencher dye (6-carboxytetramethylrhodamine). Each PCR reaction (5 µL total) will contain 10 ng of participant DNA, 30 pmol of each primer, 12.5 pmol of each TaqMan probe, and 1× TaqMan Universal PCR Master Mix (Applied Biosystems).

#### **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,<sup>67</sup> the GI-specific sub-module, QLQ-CR29,<sup>68</sup> and the EQ-5D health utilities index.<sup>69,70</sup> 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.<sup>71</sup>

### **5. STUDY DRUG INFORMATION**

#### **5.1. CPP-1X [Eflornithine HCl]**

Eflornithine Hydrochloride, also known as DFMO, is an inhibitor of ornithine decarboxylase (ODC) designated chemically as 2-(difluoromethyl)-DL-ornithine monohydrochloride monohydrate. The clinical dosage form is a yellow, film-coated convex tablet containing 250 mg of eflornithine HCl, monohydrate. Table 1 lists the composition of the 250 mg CPP-1X- tablets. The tablets (CPP-1X and CPP-1X-placebo) are packaged and sealed in opaque white HDPE bottles, and each bottle contains 100 tablets. The CPP-1X and CPP-1X placebo tablets are supplied by Sanofi-Aventis, Canada, Inc.

The tablets are to be stored at room temperature (20-25°C).

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

**Table 1 - Composition of CPP-1X (Eflornithine HCl), 250 mg Tablets**

Ingredients	Unit Formula (mg) Per Tablet	Reference to Standards
Active Substance: Eflornithine (Eflornithine HCl, monohydrate)	250	--
Microcrystalline Cellulose	192.85	NF
Starch 1500	53.40	NF
Colloidal Silicon Dioxide	1.25	NF
Magnesium Stearate	2.50	NF
<b>Total Theoretical Weight</b>	500	--

### 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 U.S., and the formulation used in this trial is similar to that used in the Phase III colon adenoma clinical trial in combination with sulindac.<sup>41</sup>

**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<sup>2</sup> 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.<sup>33</sup>

**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.<sup>33</sup>

**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 steroidogenesis.<sup>72</sup> 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,<sup>73</sup> Haegele *et al.*, 1981,<sup>74</sup> Meyskens, *et al.*, 1998,<sup>35</sup> and Meyskens *et al.*, 2008.<sup>41</sup>

## **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. Table 2 lists the composition of the 150 mg tablets. 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. Sulindac and sulindac placebo will be supplied by Watson Pharmaceutical, Inc., Corona, CA.

The tablets are to be stored at room temperature (20-25°C).

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

**Table 2 - Composition of Sulindac 150 mg Tablets**

<b>Ingredients</b>	<b>Unit Formula (mg) Per Tablet</b>	<b>Reference to Standards</b>
Active Substance: Sulindac	150	USP
Microcrystalline Cellulose	80.63	NF
Starch	18	NF
Purified Water	*	USP
Stearic Acid	3.82	NF
Magnesium Stearate	2.55	NF
<b>Total Theoretical Weight</b>	255	--

\* = Used in manufacturing process, but does not appear in the final product.

### **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 arteriosus) 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 (Watson Laboratories, Inc.)<sup>63</sup> for additional information.

#### **5.2.2. Sulindac Pharmacokinetics**

Refer to the Sulindac product insert (Watson Laboratories, Inc.)<sup>63</sup> 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  $3.9 \pm 2.3$  hours, and  $5.85 \pm 4.5$  hours for the sulfone metabolite and  $6.2 \pm 3.1$  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),  $\geq 18$  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, except for clinical polyposis, 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 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  $3,000/\text{mm}^3$
  - c) Platelet count at least  $100,000/\text{mm}^3$
  - 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\*.
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 mg daily aspirin or 650 mg aspirin not more than once a week are eligible.
17. No concurrent warfarin, fluconazole, lithium, Pradaxa<sup>®</sup> or other direct thrombin inhibitors, Plavix<sup>®</sup>, cyclosporine, other NSAIDs (such as ibuprofen, aspirin, diflunisal), diuretics (furosemide and thiazides), DMSO, methotrexate, probenecid, propoxyphene hydrochloride, Tylenol<sup>®</sup> (acetaminophen) preparations containing aspirin or cytotoxic chemotherapy drugs.
18. Willingness to forego concurrent use of supplements containing omega-3 fatty acids, corticosteroids, non-steroidal anti-inflammatory drugs or other FAP directed drug therapy.
19. Able to provide informed consent and follow protocol requirements.

\*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 for the duration of the study and for at least 2 weeks afterwards.

## 6.2. Exclusion Criteria

1. Prior pelvic irradiation.
2. Patients receiving 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 650 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 at high cardiovascular disease risk are not eligible for study participation as defined below.

“High risk” for cardiovascular disease is defined as:

- Clinical diabetes mellitus (Type I or II) requiring glycemic medications, or
  - Prior personal history of cardiovascular disease – heart attack, stroke, transient ischemic attack, or symptomatic peripheral vascular disease, or two of the following:
    - Taking anti-hypertensive medication
    - Taking lipid lowering medication
    - Current cigarette smoker
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. Colon/rectum/pouch with high grade dysplasia or cancer on biopsy or a large polyp (>1 cm) not amenable to complete removal.
  11. Duodenal cancer on biopsy.
  12. Intra-abdominal desmoid disease, stage III or IV (staging criteria in Appendix C).<sup>9,75</sup>
  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**

Patients 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. Patients 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 time to any defined FAP-related event in the patient 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. Patient 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**

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

### **FAP Study Schedule Footnotes**

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

- <sup>1</sup>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.
- <sup>2</sup>Chemistry panel includes – electrolytes (Na, K, CL, CO<sub>2</sub>), liver function tests (AST, ALT, Alkaline phosphatase, bilirubin), BUN, creatinine.
- <sup>3</sup>CBC – hemoglobin, hematocrit, WBC, platelet count, automated differential.
- <sup>4</sup>Vital signs – temperature, blood pressure, pulse, respirations, body mass index calculation.
- <sup>5</sup>Complete Physical Exam – including height (baseline only), weight, vital signs.
- <sup>6</sup>Audiometry will need to be done using air conduction methodology.
- <sup>7</sup>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).
- <sup>8</sup>Medications and patient 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.
- <sup>9</sup>Patients are to record in their 3-month diaries: medication use, presence of symptoms, and a self-assessment of presence of gross blood or melena.
- <sup>10</sup>Lower GI (LGI) endoscopy (proctoscopy or colonoscopy) will be done on all randomized patients.
- <sup>11</sup>During the LGI procedure, normal mucosal biopsy for polyamine analysis will be obtained at; screening/baseline, 6 months and 24 months/EOT.
- <sup>12</sup>On-study Upper GI (UGI) endoscopy will be done on all randomized patients.
- <sup>13</sup>Monthly ( $\pm$  7 days) phone/email contact by the study coordinator to follow-up on medication/drug compliance review, concomitant medications, and adverse events.
- <sup>14</sup>The follow-up will be done as phone call to the patient to review medical history, surgical history for any FAP-related surgical events, concomitant medications and adverse events.
- <sup>15</sup>A food frequency recall questionnaire will be administered at the screening/baseline, 12 and 24 month/EOT visits.
- <sup>16</sup>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.
- <sup>17</sup>A peripheral blood sample (10 mL, EDTA) will be collected at screening/baseline for pharmacogenomic analysis.
- <sup>18</sup>A random urine sample (15 mL minimum) will be collected at the screening/baseline, 12 and 24 month visits for polyamine analysis.
- <sup>19</sup>The follow-up will be done monthly as phone call to review endoscopic excisional procedures/surgical history for any FAP-related surgical events.
- <sup>20</sup>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.
- <sup>21</sup>EOT visit will occur within 2 weeks off study treatment for any cause including completion of treatment at 24 months.
- <sup>22</sup>EKGs will need to be obtained on the day PK samples are collected at pre-dosing, and after the 4 hr PK sample has been obtained.

## **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 a 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 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 will have baseline and on-study UGI endoscopy as part of this trial.

A complete physical exam including height, weight and vital signs will be performed.

Baseline blood 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 4). 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 4 - Study Medication Schedule<sup>1</sup>**

AGENT and DOSE	ROUTE	RX INTERVAL
CPP-1X 750 mg & Sulindac 150 mg	Oral	Daily for 24 months
<b>OR</b>		
CPP-1X placebo & Sulindac 150 mg	Oral	Daily for 24 months
<b>OR</b>		
CPP-1X 750 mg & Sulindac placebo	Oral	Daily for 24 months

<sup>1</sup>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 patient diaries will be dispensed to the patient 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 patient diary.

Based on published data utilized to project event rates, patients will receive treatment for 24 months. However, interim analyses prescribed by the Data Monitoring Committee charter may result in earlier stopping based on futility or toxicity.

#### 8.2.5. Follow-up During Treatment Intervention

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

During the 24 month drug intervention, patients will be followed monthly by phone interview for assessment of possible toxicities and medication compliance. A diary of compliance and symptoms will be maintained by patients 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 patient diaries will be provided.

At the 3-month visit, patients will have a physical exam (including weight and vital signs), blood and urine samples obtained for laboratory tests (CBC, chemistry panel, urinalysis), pharmacokinetics (PK), and EKGs (pre-dosing and after the 4-hour PK sample collection). 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 visit, patients will have a physical exam (including weight and vital signs), blood samples obtained for laboratory tests (CBC, chemistry panel, urinalysis), EKG and their first on

study treatment upper and lower endoscopy procedures. A second 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. 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 12 month visit patients will have a physical exam (including weight and vital signs), blood samples obtained for laboratory tests (CBC, chemistry panel, urinalysis), audiometry testing, EKG and their second set of on study treatment endoscopy procedures. Women of child bearing potential will also have a serum pregnancy test performed. 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.

At the 18 month visit patients will have a physical exam (including weight and vital signs), blood samples obtained for laboratory tests (CBC, chemistry panel, urinalysis), EKG, and their third on study treatment endoscopy procedures. Women of child bearing potential will also have a serum pregnancy test performed. 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.

#### **8.2.6. Final Intervention Visit/End of Treatment (Month 24 +/- 2 weeks or at end of treatment +/- 2 weeks)**

Within 2 weeks off final study pill treatment for any cause, all patients will have a follow-up history and physical exam (including weight and vital signs), along with toxicity assessment. Repeat blood laboratory tests (CBC, chemistry panel, urinalysis), EKG and audiometry will be performed. Women of child bearing potential will also have a serum pregnancy test performed. 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 normal mucosa biopsy and random urinalysis for polyamine analysis) with image and video documentation will be obtained at the Month 24 visit or if the patient has completed at least 3 months of treatment from the previous on-study upper and lower endoscopy procedures (including baseline).

If the patient 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 urinalysis for polyamine analysis should be obtained if the endoscopy procedure(s) indicate that the patient will go off study treatment.

If there is a cumulative delay/suspension of study medication for greater than 90 days for any reason, the patient will need to be formally taken off-study treatment and complete the End of Treatment (EOT) assessments.

A temporary suspension from taking study medication (less than 90 days), for example, a non-FAP disease related surgery or procedure will be documented as a treatment delay and the patient will continue on study, on their original schedule.

**8.2.7. Follow-Up (30-days post end of treatment visit +/- 1 week) Off Study**

Thirty-days (30) after completion of the end of study evaluations, patients will be contacted by phone for a clinical update in regard to symptoms and interval medical history. The patient 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. Follow-Up (Months 2-6, each month +/- 1 week) Off Study**

For the next 5 months after the 30 day follow-up, if the patient 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, patients 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. Definition of FAP-Related Events or Serious and Unexpected Toxicity

The first 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<sup>^</sup> 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  $\geq 10$  mm in size (per pathology report) and/or pathologic evidence of high grade dysplasia.\*
  - b) Disease progression<sup>^</sup> indicating need for proctectomy
  - c) Disease progression<sup>^</sup> 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, 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.

<sup>^</sup>Disease progression is based on endoscopic evaluations compared to baseline demonstrating a clinically significant increase in number and/or size of polyps, 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,  $\geq$  grade 3
- Tinnitus  $\geq$  grade 2, or clinical hearing impairment  $\geq$  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.

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 4.0.

If a patient 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 patients 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 or until the event resolves.

### **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.

Participant treatment will be unblinded only if the study physician demonstrates a compelling medical need for this information. Specifically, we expect that unblinding of an individual study subject's treatment assignment may occur if in the opinion of the Investigator, and the Medical Monitor, identification of the study medication is necessary to protect the welfare of the subject. The study Medical Monitor must approve the request verbally and later in writing prior to unblinding to ensure that reasons for the unblinding are adequate. The Medical Monitor is a Sponsor representative who has medical authority for the evaluation of the safety aspects of the clinical trial. The study drug may be discontinued without unblinding the participant.

#### **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 8.2.9.
2. Clinical reduction in hearing acumen requiring use of a hearing aid.
3. Pregnancy while on treatment, see Section 11.8.
4. 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.
5. Cumulative delay of study intervention > 90 days for any reason.
6. Completion of 24 months intervention. Duration of intervention will be 24 months from the first day of study treatment initiation regardless study visit and or procedure delays.
7. At the request of the Sponsor in situations such as protocol violations or concerns about the patient's safety.
8. The patient is lost to follow-up.
9. The patient may withdraw from the study-treatment at any time for any reason.
10. Patient death.

### 8.3.3. Protocol Withdrawal (Off-Study)

1. The patient 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 polyps > 5 mm in diameter will be removed.

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, patients will undergo repeat upper and lower endoscopy. At any interval assessment, if any subject requires an excisional intervention (as defined in Section 8.2.9), or has duodenal Spigelman stage progression, 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 a central imaging laboratory for archiving. All data will be de-identified in regard to patient, site and treatment but patient 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 patients will have blood samples obtained for pharmacokinetic studies. Pharmacokinetic sampling will occur once at the scheduled 3 month visit. Samples may be collected within  $\pm 2$  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 patient will be contacted by a study coordinator at least three (3) days prior to the scheduled visit to remind the patient to not take their morning dose of study medication on the day of the planned visit.

On the morning of the visit, upon patient arrival, it will be verified that the patient did not take their morning dose of study medication. Those patients that mistakenly took their morning dose will be sent home and rescheduled within the next week. Thereafter, a pre-dose blood sample (5 mL, lithium heparin vacutainer tube) will be collected and a pre-dose EKG will be obtained. The patient will then take their study medications in the usual manner. The patient may then leave the clinic and have their typical breakfast.

**Table 5 – Pharmacokinetic Sample Number and Sampling Times**

Sample Number	Target Time	No Earlier Than	No Later Than
1	Pre-dose*	NA	NA
2	1 hour	45 minutes	75 minutes
3	2 hours	90 minutes	150 minutes
4	4 hours*	3 hours	5 hours
5	8 hours	6 hours	10 hours

\*EKGs need to be done after the pre-dose and 4 hour samples have been 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  $\pm 15$  minutes,  $\pm 30$  minutes,  $\pm 60$  minutes (1 hour),  $\pm 120$  minutes (2 hours),

respectively, keeping in mind that the third and fourth samples must be at least one hour apart. 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)**

Patient 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 the 6 month and 24 month 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 patients 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**

Patients 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 patients 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 Patient Preferences

For this study, we plan to use four (4) instruments to measure HRQoL and patient 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<sup>67</sup> 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<sup>68</sup> 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.<sup>69,70</sup> It provides a simple descriptive profile and a single index value for health status.
- The Cancer Worry Scale<sup>71</sup> 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 and at 3, 6, 12, 18, and 24 months post-enrollment/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 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.

In addition to the HRQoL assessment, patient preferences (or utilities) will also be assessed. Data will be collected at baseline and at 3, 6, 12, 18, and 24 months post-enrollment/end of treatment and preference weights among the treatment arms will be determined using the EuroQol EQ-5D assessment of individual health states.<sup>69,70</sup> 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 and at 3, 6, 12, 18, and 24 months post-enrollment/end of treatment and it will be scored according to the guidance provided by Lerman *et al.*<sup>71</sup>

## **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.<sup>76,77</sup> Data from the FFQ will be analyzed using a polyamine database<sup>66</sup> 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, 12 months and 24 months/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<sup>78</sup> 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.*<sup>40</sup> could lead to dietary restrictions in combination with the combined eflornithine-sulindac therapy.

## **11. ASSESSMENT OF SAFETY**

### **11.1. Cardiac Risk**

All patients will undergo a baseline medical history evaluation and EKG for cardiovascular disease risk assessment. Only subjects meeting the inclusion criteria will be enrolled in the study. On-study cardiac risk assessments, for each patient, will take place throughout the study via ongoing adverse event assessments and periodic EKG evaluations at baseline, and months 3, 6, 12, 18 and 24 (end of treatment).

### **11.2. Ototoxicity Risk**

All patients will undergo air conduction audiometry for hearing impairment as part of the screening process and at months 12 and 24 (end of treatment). Patient diaries will indicate the presence of symptoms and will instruct the patient to contact the treating doctor for assessment. These data will not be used to exclude patients from this study.

At the 3, 6, 12, 18 and 24 month visits, the patient will undergo a clinical assessment for ototoxicity adverse events symptoms by the research nurse or other medically qualified individual.

### **11.3. Gastrointestinal Risk**

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

At the 3, 6, 12, 18 and 24 month visits, the patient will undergo a clinical assessment for gastrointestinal adverse events symptoms by the research nurse or other medically qualified individual.

#### **11.4. Safety Parameters**

Patients 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 4.0, ([http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03\\_2010-06-14\\_QuickReference\\_5x7.pdf](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 patient 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 patient's condition.

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.

### **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 patient at immediate risk of death);
3. Requires inpatient 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 patient 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 patient 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. All adverse experiences, including duration and severity will be captured in the Case Report Forms provided by the Sponsor.

#### **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, Health 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 patient is pregnant or may have become pregnant at the time of investigational drug exposure, the investigational drug will be permanently discontinued. 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. All study required procedures for study discontinuation and follow-up must be completed unless contraindicated by the pregnancy. 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 will be coded to therapeutic drug classes and generic names using for example the WHO Drug classification dictionary.

Patients are to be instructed to not take the following medications or supplements while on study treatment: corticosteroids (such as prednisone), NSAIDS (such as ibuprofen, celecoxib, aspirin, diflunisal), supplements containing omega-3-fatty acids (such as fish oil), anticoagulants (such as warfarin, Pradaxa<sup>®</sup>, and Plavix<sup>®</sup>) or other direct thrombin inhibitors), fluconazole, lithium, furosemide and thiazides, DMSO, methotrexate, probenecid, propoxyphene hydrochloride, Tylenol<sup>®</sup> (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 to the first FAP-related event in Familial Adenomatous Polyposis (FAP) patients. Eligible patients who have given informed consent will enter the study the intent to participate for the full treatment period of 24 months. Accrual is expected to take 6 – 12 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.

A total of 150 eligible patients will be enrolled in this study, 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 patients 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 patients who have signed a voluntary and fully informed consent form, have been deemed eligible to participate by the Investigator based on the screening assessments, and have been randomized to one of the three study arms. Patients 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 patients 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 time to the first occurrence of any FAP-related event. Section 8.2.9 provides complete detail on FAP-related events.

Thus the primary objective contains two treatment comparisons:

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

Each comparison will be performed at the 2-sided  $p = 0.05$  level.

The decision to seek regulatory approval based upon the results of the primary objective will be taken sequentially. If the result of comparison 1 is significant at level 0.05, FDA approval will be sought. If comparison 1 is significant, then if the result of comparison 2 is also significant at level 0.05, EMA approval will be sought as well. But if the result of comparison 1 is not significant at level 0.05, neither FDA nor EMA approval will be sought. This procedure is formally equivalent to a closed sequential test procedure for controlling the probability of making a false claim that regulatory criteria are satisfied at level 0.05.

The analytic method for the primary analysis will be a time-to-event analysis using the log-rank test. Cox proportional hazards regression models will be used for secondary assessments<sup>80</sup>. Graphical analyses (log-minus-log plots) will be used to check the assumption of constant hazard ratios.

For the primary analysis, two 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<sup>81</sup>. 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. Generally, a patient will be considered a treatment failure if for any reason, the endpoint determination cannot be made per the pre-specified study requirements. The time to this imputed event will be from randomization to the last recorded patient visit. A patient who is lost to follow-up for reasons deemed unrelated to his or her endpoint status will be treated as a censored observation as of the last patient visit. If a patient does not have a FAP related event at the 24 month close-out visit, the patient will be treated as a censored observation as of the actual follow-up time for the close-out visit.

### **12.2. Secondary Efficacy Outcome and Analysis**

The secondary efficacy outcome in this study will include the following:

1. To evaluate the potentially effect modifying properties of :
  - a. Presence or absence of an ODC polymorphism
  - b. The excretion of 4 urinary polyamines (diacetylspermine, n1-acetylspermidine, n8-acetylspermidine and decarboxylated SAM)

These five secondary variables will be assessed regardless of study outcome, but their use as potential label claims will only apply if a statistically significant treatment effect is found in the primary analysis. For the secondary efficacy analysis, for each secondary variable, a corresponding term will be added to the primary analysis as well as an interaction term (product of the treatment indicator and secondary variable). The coefficient of the interaction term (only) will be tested to determine if the secondary variable alters the magnitude of the treatment effect. Corresponding to each of the two primary analyses, the Hochberg step-up method<sup>82</sup> will be employed to control the overall family-wise error rate with overall alpha set at the two-sided 0.05 level.

### **12.3. Other Secondary Outcomes**

Other secondary outcomes will include the following:

1. Safety outcomes will be assessed by summary analysis of adverse events and clinical laboratory abnormalities.
2. Pharmacokinetic outcomes will be assessed by evaluating the population pharmacokinetics for CPP-1X (eflornithine) and sulindac.
3. Evaluate tissue and dietary polyamine levels.
4. Patient reported quality of life will be evaluated using HRQoL and patient utilities.

5. A pilot evaluation of an FAP-specific assessment, the time to the first FAP-related beneficial event, will be studied. This will involve analyzing the endoscopic polyposis data for regression of pre-colectomy colorectal polyposis, rectal/pouch polyposis, and regression of duodenal polyposis.
6. An analysis of the components and subgroups included in the primary analysis, and their contribution to the primary outcome.

#### **12.4. Sample Size Determination**

For the purposes of power calculations, we assume the following:

- 1) The level of statistical significance is set at 0.05, using a 2-sided log-rank test for time-to-first FAP-related event, for each of the two between-group comparisons (i.e. CPP-1X + sulindac vs. CPP-1X and CPP-1X plus sulindac vs. sulindac);
- 2) A doubling of the time to occurrence of the primary event 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 the combination arm vs. either of the two single treatment arms;
- 4) The two single-agent treatment groups have the same event rate.

For this situation, 49 events would be needed for the two-group situation at the 2-sided 0.05 level with 85% power and the doubling of the time to primary event.<sup>79</sup> Assuming two-year event proportions of 70% in either of the two single-agent groups and 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 20 in the combination arm. Thus we expect to have 55 patients with a FAP related event in each comparison, achieving almost 89% power. The standard deviation around this expectation is 4.74, so we would be highly likely to observe at least the required 49 events. Even if the total number of events in either comparison were only 43, there will still be 80% power to detect the design effect size, namely, a hazard rate ratio of  $0.4243 = (\ln 0.60)/(\ln 0.30)$  corresponding to the doubling of event-free follow-up over two years.

In total we expect to observe  $35+35+20=90$  primary endpoints among the three groups (plus or minus 5.7). To achieve this number of events, we plan to have a 3 year study (with up to 12 months enrollment assuming no sample size reassessment plus 2 years of treatment and follow-up for the last-enrolled patients).

This is based on our review of limited single-agent data for eflornithine and sulindac, in which the 2-year event free rates imply a single overall event free rate of 60% for combination treatment group and 30% in each single agent treatment group.

#### **12.5. Populations for Analysis**

##### **12.5.1. Intent-to-Treat (ITT) Population**

The intent-to-treat population includes all patients who have signed a voluntary and fully informed consent form, have been deemed eligible to participate by the Investigator based on the screening assessments, and 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 who completed all 24 months of treatment and has primary endpoint determinations performed per protocol specifications.

### **12.5.4. Other Populations**

Within the entire patient population there will be subsets who did not receive 24 months of daily medication. The patient diary and pill count will define the extent of compliance. This subgroup of patients will be categorized into various groups only for purposes of exploratory and sensitivity analysis including:

- Patient 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 and the institution at which each patient registered, 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).<sup>83</sup>

### **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.

Patient disposition and treatment will be summarized for ITT and safety populations defined previously. Patient disposition will be consistent with the CONSORT criteria,<sup>84</sup> and will include per treatment group enumeration of all patients randomized, number ineligible, early termination due to AE/SAE, the number of subjects with an SAE, deaths, dropout for other reasons, and the number of subjects lost to follow-up. Additional summaries will include reasons for patients discontinuing treatment and/or modifying treatment dosages, and a summary of patients' treatment status. 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 test will be used to reflect the stratified randomization. Exact p-values and 95% confidence intervals by the point probability method will be reported<sup>85</sup>.

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.<sup>83</sup>

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). 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 within each level of randomization strata separately.

### **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 at 3, 6, 12, 18, and 24 months post-enrollment/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.<sup>69,70</sup> 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*<sup>71</sup>.

This trial has three strata and three treatment options with 150 patients to be entered. HRQoL data will be obtained while patients are receiving treatment. 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.<sup>76,77</sup> Data from the FFQ will be analyzed using a polyamine database<sup>66</sup> 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, 12 months and 24 months/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<sup>78</sup> that indicate consumption of a diet high in polyamines is associated with reduced treatment efficacy.

#### **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. A patient will be considered a treatment failure if for any reason, the endpoint determination cannot be made per the pre-specified protocol. The time to this imputed event will be from randomization to the last recorded patient visit. Any secondary or sensitivity analysis that includes this assumption will be clearly noted. Similarly, any sensitivity analysis that incorporates the last observation carried forward (LOCF) method, to compensate for early patient dropouts or missing data, will be clearly noted.

Secondary analysis data include the presence of a specific genetic mutation, and urinary metabolite concentrations (see Section 12.2). The primary analysis of the secondary objectives will include collected data only, without imputing or weighting data to compensate for missing data. 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* (September, 1998)”.

All available efficacy and safety data will be included in data listings and tabulations. Data that are potentially spurious or erroneous 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 at a later time 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 (A versus B) 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, 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 (based on a blinded A/B comparison).

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 perform an assessment of 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 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. With this approach study enrollment can continue uninterrupted at the study sites, if it is decided to increase study sample size.

The futility assessment will occur when approximately 50% of maximum trial information has been amassed. Assuming a constant enrollment rate over 1 year and full enrollment achieved at one year, that would occur at approximately 1.5 years from enrollment start. At that time patients would have an average of approximately 1.0 year on study treatment. Unless the DMC requires it on ethical grounds, no early stopping for positive efficacy is proposed.

## 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](http://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. Patients 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 patient vomits within an hour after taking the tablets, the patient will record a missed dose in the diary. If the patient 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 patient 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 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 patients on the study and remove current patients 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 patient 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 patient 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 patient records. Patient 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
BCA	Bicinchoninic acid
BID	Twice a day
<sup>0</sup> 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, difluoromethylornithine
CRC	colorectal cancer
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
dB	Decibels
DFMO	Eflornithine, CPP-1X, difluoromethylornithine
dL	deciliter
DMC	Data Monitoring Committee
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic Acid
DSMB	Data Safety and Monitoring Board
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
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 polyethylene
HGD	High grade dysplasia
HRQoL	Health-Related Quality of Life
IB	Investigator's Brochure
ICH	International Committee on Harmonization

IME	Important medical event
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	Intrauterine device
IUS	Intrauterine system
LGI	Lower gastrointestinal
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
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
ULN	Upper limit of normal
US	United States
T <sub>1/2</sub>	Half-life
WBC	White Blood Cell
WHO	World Health Organization

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## APPENDIX A SPIGELMAN'S SCORE AND STAGE

### Modified Spigelman's Score and Classification (Saurin, 2004)

	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 cribriformed in architecture but still all located above the basement membrane.

### Vienna Classification of Gastrointestinal Epithelial Neoplasia (Schlemper *et al.*, 2000)

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 <ul style="list-style-type: none"> <li>4.1 High grade adenoma/dysplasia</li> <li>4.2 Non-invasive carcinoma (carcinoma in situ)<sup>a</sup></li> <li>4.3 Suspicion of invasive carcinoma</li> </ul>
Category 5	Invasive neoplasia <ul style="list-style-type: none"> <li>5.1 Intramucosal carcinoma<sup>b</sup></li> <li>5.2 Submucosal carcinoma or beyond</li> </ul>

<sup>a</sup>Non-invasive indicated absence of evident invasion.

<sup>b</sup>Intramucosal indicated invasion into the lamina propria or muscularis mucosae.

## APPENDIX B InSiGHT RECTUM/POUCH ASSESSMENT AND STAGE

Stage	Polyp Description	Recommended Intervention	Comment
<b>0</b>	0-10 polyps, all <5mm	Repeat FS in 1 years	
<b>1</b>	10-25 polyps most <5mm, none >1cm	Ablate polyps; repeat sigmoidoscopy in 1 year	Chemopreventive may be considered
<b>2</b>	10-25 polyps, any >1cm, amenable to complete removal	Repeat sigmoidoscopy 6 months  Polypectomy preferred	Removal of large polyps clearly necessary  Chemopreventive valuable
<b>3</b>	> 25 polyps amenable to complete removal, or any incompletely removed sessile polyp, or any 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
<b>4</b>	>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

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## **APPENDIX C      Desmoid Staging System**

<b>Stage</b>	<b>Description</b>
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.

## APPENDIX D 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
<p>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</p>	<ul style="list-style-type: none"> <li>80% of patients develop adenomas within the pouch body.</li> <li>71% ↓ of adenomas after 4-6 mo. Sulindac (300-400mg/day)-analysis combined randomized studies.</li> <li>Incidence of pouch adenomas is time-dependent with 42% of patients at 7 yrs from pouch construction.</li> <li>Median time from pouch construction to diagnosis pouch adenomas, 4.7 yrs (0.5-12 yrs).</li> <li>Celecoxib treated patients, median time to first polypectomy post IRA was 18.69 months; 90.9% (30 patients) had a post IRA rectal polypectomy.</li> <li>Celecoxib treated patients, post IPAA, 3 of 24 pts (12.5%) had post IPAA polypectomy, 21 censored. 25<sup>th</sup> and 50<sup>th</sup> percentiles of time to first polypectomy in IPAA patients was 169.9 months</li> </ul>	<ul style="list-style-type: none"> <li>80% of patients develop adenomas within the pouch body.</li> <li>Celecoxib treated patients, median time to first polypectomy post IRA was 18.69 months; 90.9% (30 patients) had a post IRA rectal polypectomy.</li> </ul> <div> <p><b>Summary Projected 2 year Event Rate: Excisional intervention and/or high risk adenoma – 40-60%</b></p> </div>
Duodenal Disease		
Key References	Comments	Event/Rate
<p>Bulow, et al., Gut, 2004            Bulow, et al., Familial Cancer, 2011            Brosens, et al., Gut 2005            Cruz-Correa, et al., Gastroenterology, 2002            Church, Surg Onc. Clin N Am, 2009            Clark, et al., Familial Cancer, 2011            Groves, et al., Gut, 2002            Johnson, et al., Gastrointest Surg, 2010            Phillips, et al., Gut 2002            Saurin, et al., JCO, 2004            Vasen, et al., Gut, 2008            van Heumen, et al., Familial Cancer, 2011</p>	<ul style="list-style-type: none"> <li>95-100% of all FAP patients develop duodenal adenomas</li> <li>10-25% of patients have Stage III/IV</li> <li>36% of Spigelman Stg IV develop cancer</li> <li>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%.</li> <li>Patients down staged from Spigelman stage IV demonstrate increased rate of disease progression back to severe disease.</li> </ul>	<ul style="list-style-type: none"> <li>Recurrence rate of adenoma development is <math>\geq 50\%</math> after endoscopic treatment and treatment is associated with 17% complication rate (perforation, hemorrhage, pancreatitis)</li> <li>Rate of progression between Spigelman stages variable, 4 – 11 yrs</li> </ul> <div> <p><b>Summary Projected 2 Year Event Rate: Excisional intervention, cancer – 50%</b></p> </div>
Pre-Colectomy		
	Comments	Event/Rate
	<ul style="list-style-type: none"> <li>Diagnosis with recommendation to proceed with prophylactic colectomy or proctocolectomy.</li> </ul>	<div> <p><b>Summary Projected 2 Year Event Rate: Excisional intervention, cancer – 90%</b></p> </div>

**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)**

**EudraCT Number: 2012-000427-41**

**NCT Number: 01483144**

**Date: 17January2019**

**Version: 5.2**

**Sponsored by  
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## INVESTIGATOR PROTOCOL AGREEMENT

### CPP FAP-310

#### 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)

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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## 1.6. Study Schema

### MAJOR ELIGIBILITY CRITERIA

1. Diagnosis of Familial Adenomatous Polyposis (FAP) with confirmed APC mutation AND age  $\geq 18$  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

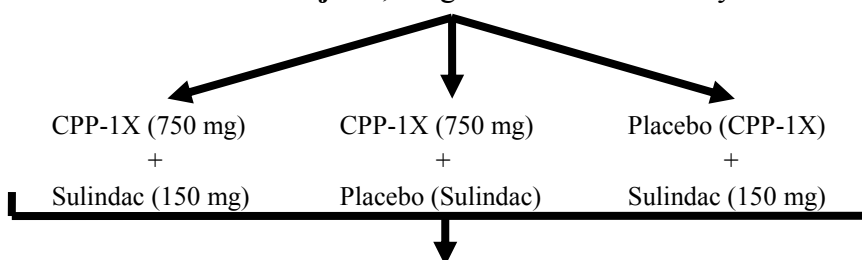
Stratification based on FAP-related time to first event prognosis.

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<sup>®</sup>, (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)<sup>1</sup> can accurately predict those with adenomas that are most likely to progress to cancer. Bulow and colleagues<sup>2</sup> 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.<sup>3-6</sup> 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.<sup>7-9</sup> Although an important site of disease and morbidity for FAP patients, this protocol will focus on intestinal polyposis only.

Vasen and colleagues<sup>10</sup> 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  $\geq 1$  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.<sup>11-15</sup> The biology of common colorectal cancer is similar to the FAP phenotype. Wallace and Lynch<sup>16</sup> 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<sup>17</sup> 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<sup>18</sup> 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<sup>19</sup> 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.*,<sup>20</sup> 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<sup>21</sup> 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<sup>22</sup> 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.<sup>23,24</sup> 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.<sup>25,26</sup> Patients were randomized to placebo control, celecoxib 100 mg twice daily, and celecoxib 400 mg twice daily. In the Steinbach report,<sup>25</sup> 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.<sup>27,28</sup>

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<sup>2</sup>), 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.<sup>29-31</sup>

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.<sup>28</sup> 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.<sup>32</sup> In a second study, 291 people with prior non-melanoma skin cancers were treated with eflornithine alone (500 mg/m<sup>2</sup> 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.<sup>33</sup> 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.<sup>34</sup> 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.<sup>35</sup> 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<sup>36,37</sup> and sporadic breast cancer<sup>38</sup>. In addition, two independent groups have reported that this same polymorphism is associated with prostate cancer<sup>39</sup> and colon cancer survival.<sup>40</sup>

### **2.3. Sulindac and Eflornithine; Colorectal Polyp Chemoprevention**

Meyskens and colleagues<sup>41</sup> 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.<sup>42,43</sup> ODC enzyme activity and polyamine contents are elevated in the apparently normal colonic mucosa of genotypic FAP patients, compared to FAP normal family members.<sup>44</sup> 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.<sup>45</sup> Studies in animal models of FAP indicate that eflornithine alone is effective in reducing the number of intestinal<sup>29</sup> and colonic<sup>30</sup> 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.<sup>46</sup> Combination treatment with eflornithine and sulindac dramatically reduce the incidence of metachronous colorectal adenomas in patients with prior sporadic adenomas.<sup>41</sup> 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.<sup>31</sup> 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<sup>2</sup>/day.<sup>47</sup> 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<sup>2</sup>/day as a dose range that effectively reduced colorectal tissue polyamine contents.<sup>35</sup> Oral doses in this range achieve serum concentrations that inhibit ornithine decarboxylase enzyme activity and polyamine synthesis in cell culture models.<sup>48</sup> 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 polyps.<sup>41</sup> Based on an average adult body surface area of 1.6 m<sup>2</sup>,<sup>49</sup> 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.<sup>41,50</sup> 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.<sup>34</sup>

Recently, a clinical trial of eflornithine in combination with another NSAID for prevention of polyps in FAP patients has been reported. Lynch *et al.*<sup>27,28</sup> have reported results of a trial using 500 mg/m<sup>2</sup>/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<sup>2</sup>/day eflornithine for 4-5 years.<sup>33</sup> 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.<sup>33</sup>

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.<sup>44</sup> These levels are higher than those reported for patients with sporadic risk of colorectal cancer.<sup>51</sup>

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.<sup>28,33</sup> The Lynch study provides evidence for efficacy of the higher eflornithine dose in FAP patients.<sup>28</sup>

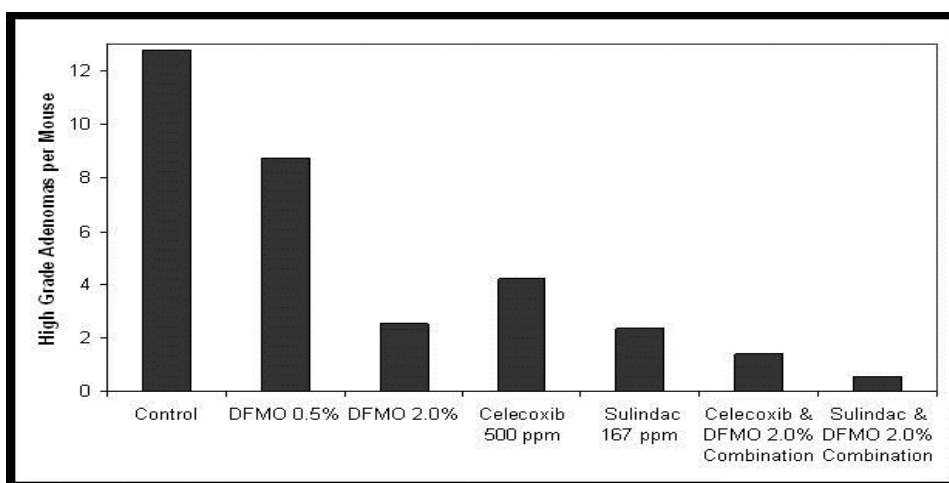
## 2.6. Rationale for Sulindac Dose

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.<sup>43</sup> 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.<sup>52</sup>

Eflornithine-sulindac combinations are potent inhibitors of intestinal carcinogenesis in mouse models,<sup>31</sup> 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<sup>53</sup> 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,<sup>54</sup> 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<sup>20,21,55,56,57,58</sup> 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.<sup>59</sup> 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.<sup>55</sup> 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<sup>60</sup> – 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<sup>61</sup> 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.<sup>61</sup> 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<sup>41</sup>, 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.<sup>34</sup>

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.<sup>41</sup> 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.<sup>27,28</sup> Bailey and colleagues have recently updated their study of patients with prior non-melanoma skin cancer that were treated with 500 mg/m<sup>2</sup> (also rounded to the nearest 250 mg as they used eflornithine tablets) for 4-5 years.<sup>62</sup> The Bailey study demonstrated a significant (P < 0.05) increase in uniformly transient audiometric (but not clinically detectable) hearing loss in participants on eflornithine.<sup>33</sup> The follow-up study did not report any clinically significant differences in hearing as compared to the placebo group.<sup>62</sup>

### **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.)<sup>63</sup> and the recent FDA Drug Safety Communication<sup>64</sup> 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<sup>2</sup> 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.<sup>10</sup> The marginal benefit of endoscopic management of the duodenum is reviewed and tabulated (Table 4) in the paper by Brosens and colleagues.<sup>65</sup> 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<sup>66</sup>. 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.<sup>67</sup>

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  $\geq 18$  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°C freezer. Random urine samples (15 mL minimum) will be collected and stored in a -70 – 80°C freezer.

Polyamine content: Polyamine analysis will be performed as described previously.<sup>35</sup> 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.<sup>35,68</sup>

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.<sup>69</sup>

#### **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,<sup>70</sup> the GI-specific sub-module, QLQ-CR29,<sup>71</sup> and the EQ-5D health utilities index.<sup>72,73</sup> 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.<sup>74</sup>

## 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).

Table 1 lists the composition of the 250 mg CPP-1X tablets. The tablets (CPP-1X and CPP-1X-placebo) are packaged and sealed in opaque white HDPE bottles, and each bottle contains 100 tablets. The CPP-1X and CPP-1X placebo tablets are supplied by Sanofi-Aventis, Canada, Inc.

The tablets are to be stored at room temperature (20-25°C).

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

**Table 1 - Composition of CPP-1X (Eflornithine HCl), 250 mg Tablets**

Ingredients	Unit Formula (mg) Per Tablet	Reference to Standards
Active Substance: Eflornithine (Eflornithine HCl, monohydrate)	250	--
Microcrystalline Cellulose	192.85	NF
Starch 1500	53.40	NF
Colloidal Silicon Dioxide	1.25	NF
Magnesium Stearate	2.50	NF
<b>Total Theoretical Weight</b>	500	--

#### 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. The formulation used in this trial is similar to that used in the Phase III colon adenoma clinical trial in combination with sulindac.<sup>41</sup>

**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<sup>2</sup> 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.<sup>33</sup>

**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.<sup>33</sup>

**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 steroidogenesis.<sup>75</sup> 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,<sup>76</sup> Haegele *et al.*, 1981,<sup>77</sup> Meyskens, *et al.*, 1998,<sup>35</sup> and Meyskens *et al.*, 2008.<sup>41</sup>

#### 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]-1H-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. Table 2 lists the composition of the 150 mg tablets. 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. Sulindac and sulindac placebo will be supplied by Actavis, formerly Watson Pharmaceutical, Inc., Corona, CA. 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°C).

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

**Table 2 - Composition of Sulindac 150 mg Tablets**

<b>Ingredients</b>	<b>Unit Formula (mg) Per Tablet</b>	<b>Reference to Standards</b>
Active Substance: Sulindac	150	USP
Microcrystalline Cellulose	80.63	NF
Starch	18	NF
Purified Water	*	USP
Stearic Acid	3.82	NF
Magnesium Stearate	2.55	NF
<b>Total Theoretical Weight</b>	255	--

\* = Used in manufacturing process, but does not appear in the final product.

### **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 arteriosus) 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.)<sup>78</sup> for additional information.

### **5.2.2. Sulindac Pharmacokinetics**

Refer to the Sulindac product insert (Actavis, formerly Watson Laboratories, Inc.)<sup>78</sup> 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  $3.9 \pm 2.3$  hours, and  $5.85 \pm 4.5$  hours for the sulfone metabolite and  $6.2 \pm 3.1$  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),  $\geq 18$  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  $3,000/\text{mm}^3$
  - c) Platelet count at least  $100,000/\text{mm}^3$
  - 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<sup>®</sup> or other direct thrombin inhibitors, Plavix<sup>®</sup>, cyclosporine, other NSAIDs (such as ibuprofen, aspirin in excess of 700 mg weekly, diflunisal), diuretics (furosemide and thiazides), DMSO, methotrexate, probenecid, propoxyphene hydrochloride, Tylenol<sup>®</sup> (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)  $\geq 12$  months spontaneous amenorrhea; b) 6 months spontaneous amenorrhea with serum FSA levels  $> 30$  IU/L<sup>79,80</sup>; c)  $\geq 6$  weeks postsurgical bilateral oophorectomy; d)  $\geq 6$  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  $\geq 190$  mg/dL or triglycerides  $\geq 500$  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).<sup>9,81</sup>
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 <sup>21</sup>	(± 1 wk)	
Informed Consent	X																X <sup>26</sup>		
Polypsis History <sup>1</sup>	X																		
Medical History <sup>24</sup>	X		X		X				X				X				X	X <sup>14</sup>	
GI Symptoms	X		X		X				X				X				X	X <sup>14</sup>	
Surgical History	X																	X <sup>14</sup>	X <sup>19</sup>
Concomitant Medications	X	X <sup>13</sup>	X	X <sup>13</sup>	X	X <sup>13</sup>	X <sup>13</sup>	X <sup>13</sup>	X	X <sup>13</sup>	X <sup>13</sup>	X <sup>13</sup>	X	X <sup>13</sup>	X <sup>13</sup>	X <sup>13</sup>	X	X <sup>14</sup>	
Drug Compliance Review		X <sup>13</sup>	X	X <sup>13</sup>	X	X <sup>13</sup>	X <sup>13</sup>	X <sup>13</sup>	X	X <sup>13</sup>	X <sup>13</sup>	X <sup>13</sup>	X	X <sup>13</sup>	X <sup>13</sup>	X <sup>13</sup>	X		
Adverse Events		X <sup>13</sup>	X	X <sup>13</sup>	X	X <sup>13</sup>	X <sup>13</sup>	X <sup>13</sup>	X	X <sup>13</sup>	X <sup>13</sup>	X <sup>13</sup>	X	X <sup>13</sup>	X <sup>13</sup>	X <sup>13</sup>	X	X <sup>14</sup>	
Chemistry Panel <sup>2</sup>	X		X		X				X				X				X		
CBC <sup>3</sup>	X		X		X				X				X				X		
Urinalysis <sup>25</sup>	X		X		X				X				X				X		
Vital Signs <sup>4</sup>	X		X		X				X				X				X		
Physical Exam/Review of Systems <sup>5</sup>	X		X		X				X				X				X		
Audiometry <sup>6</sup>	X								X								X		
EKG <sup>22</sup>	X		X <sup>23</sup>		X				X				X				X		
Serum Preg. Test <sup>7</sup>	X		X		X		X <sup>7</sup>		X		X <sup>7</sup>		X		X <sup>7</sup>		X		
Dispense Medications <sup>8</sup>		X <sup>8</sup>	X		X		X <sup>8</sup>		X		X <sup>8</sup>		X		X <sup>8</sup>				
Subject Diary <sup>9</sup>		X	X		X		X		X		X		X		X				
Food Frequency Questionnaire <sup>15</sup>	X								X								X		
LGI Endoscopy <sup>10</sup>	X				X				X				X				X		
Normal Mucosa Biopsy <sup>11</sup>	X				X				X				X				X		
UGI Endoscopy <sup>12</sup>	X				X				X				X				X		
Pharmacokinetics Blood Samples			X <sup>16</sup>																
Pharmacogenomic Blood Sample	X <sup>17</sup>																		
Polyamine Urine Samples <sup>18</sup>	X				X				X				X				X		
HRQoL surveys <sup>20</sup>	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.

- <sup>1.</sup> 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.
- <sup>2.</sup> Chemistry panel includes – electrolytes (Na, K, CL, CO<sub>2</sub>), liver function tests (AST, ALT, Alkaline phosphatase, bilirubin), BUN/urea, creatinine.
- <sup>3.</sup> CBC panel includes – hemoglobin, hematocrit, WBC, platelet count, automated differential.
- <sup>4.</sup> Vital signs – temperature, blood pressure, pulse, respirations.
- <sup>5.</sup> 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.
- <sup>6.</sup> Audiometry will need to be done using air conduction methodology (250, 500, 1000, 2000, 4000 and 8000 Hz).
- <sup>7.</sup> 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).
- <sup>8.</sup> 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.
- <sup>9.</sup> 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.
- <sup>10.</sup> Lower GI (LGI) endoscopy (proctoscopy or colonoscopy) will be done on all randomized subjects that have an intact colon or rectum/pouch.
- <sup>11.</sup> 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.
- <sup>12.</sup> On-study Upper GI (UGI) endoscopy will be done on all randomized subjects that have a duodenum.
- <sup>13.</sup> Monthly ( $\pm$  7 days) phone/email contact by the study coordinator to follow-up on medication/drug compliance review, concomitant medications, and adverse events.
- <sup>14.</sup> 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.
- <sup>15.</sup> A food frequency recall questionnaire will be administered at the screening/baseline, 12 and 24 month/EOT visits. US and Canada sites only.
- <sup>16.</sup> 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.
- <sup>17.</sup> A peripheral blood sample (10 mL, EDTA) will be collected at screening/baseline for pharmacogenomic analysis.
- <sup>18.</sup> 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.
- <sup>19.</sup> The follow-up will be done monthly as phone call to review endoscopic excisional procedures/surgical history for any FAP-related surgical events.
- <sup>20.</sup> 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.
- <sup>21.</sup> EOT visit will occur within 2 weeks off study treatment for any cause including completion of treatment at 24 months.
- <sup>22.</sup> Subject needs to be in the supine position for 10 minutes prior to the EKG, including EKGs collected during PK sampling.
- <sup>23.</sup> 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.
- <sup>24.</sup> 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.
- <sup>25.</sup> Urinalysis panel includes – color, clarity/appearance, specific gravity, pH, protein, glucose, ketones and blood.
- <sup>26.</sup> 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 <sup>21</sup>	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
<b>Procedures</b>		(± 1 wk)			(± 2 wks)	(± 1 wk)			(± 2 wks)	± 1 wk			(± 2 wks)	(± 1 wk)			(± 2 wks) <sup>17)</sup>	± 1 wk
Informed Consent	X																	
Medical History <sup>19</sup>					X				X				X				X	X <sup>13</sup>
GI Symptoms					X				X				X				X	X <sup>13</sup>
Surgical History																		X <sup>13</sup>
Concomitant Medications		X <sup>12</sup>	X <sup>12</sup>	X <sup>12</sup>	X	X <sup>12</sup>	X <sup>12</sup>	X <sup>12</sup>	X	X <sup>12</sup>	X <sup>12</sup>	X <sup>12</sup>	X	X <sup>12</sup>	X <sup>12</sup>	X <sup>12</sup>	X	X <sup>13</sup>
Drug Compliance Review		X <sup>12</sup>	X <sup>12</sup>	X <sup>12</sup>	X	X <sup>12</sup>	X <sup>12</sup>	X <sup>12</sup>	X	X <sup>12</sup>	X <sup>12</sup>	X <sup>12</sup>	X	X <sup>12</sup>	X <sup>12</sup>	X <sup>12</sup>	X	
Adverse Events		X <sup>12</sup>	X <sup>12</sup>	X <sup>12</sup>	X	X <sup>12</sup>	X <sup>12</sup>	X <sup>12</sup>	X	X <sup>12</sup>	X <sup>12</sup>	X <sup>12</sup>	X	X <sup>12</sup>	X <sup>12</sup>	X <sup>12</sup>	X	X <sup>13</sup>
Chemistry Panel <sup>1</sup>					X				X				X				X	
CBC <sup>2</sup>					X				X				X				X	
Urinalysis <sup>20</sup>					X				X				X				X	
Vital Signs <sup>3</sup>					X				X				X				X	
Physical Exam <sup>4</sup>					X				X				X				X	
Audiometry <sup>5</sup>									X								X	
EKG <sup>18</sup>					X				X				X				X	
Serum Preg. Test <sup>6</sup>			X <sup>6</sup>		X		X <sup>6</sup>		X		X <sup>6</sup>		X		X <sup>6</sup>		X	
Dispense Medications <sup>7</sup>	X		X <sup>7</sup>		X		X <sup>7</sup>		X		X <sup>7</sup>		X		X <sup>7</sup>			
Subject Diary <sup>8</sup>	X		X		X		X		X		X		X		X			
Food Frequency Questionnaire <sup>14</sup>									X								X	
LGI Endoscopy <sup>9</sup>					X				X				X				X	
Normal Mucosa Biopsy <sup>10</sup>					X				X				X				X	
UGI Endoscopy <sup>11</sup>					X				X				X				X	
Polyamine Urine Samples <sup>15</sup>					X				X				X				X	
HRQoL surveys <sup>16</sup>					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.

- <sup>1.</sup> Chemistry panel includes – electrolytes (Na, K, CL, CO<sub>2</sub>), liver function tests (AST, ALT, Alkaline phosphatase, bilirubin), BUN, creatinine.
- <sup>2.</sup> CBC panel includes – hemoglobin, hematocrit, WBC, platelet count, automated differential.
- <sup>3.</sup> Vital signs – temperature, blood pressure, pulse, respirations.
- <sup>4.</sup> 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.
- <sup>5.</sup> Audiometry will need to be done using air conduction methodology (250, 500, 1000, 2000, 4000 and 8000 Hz).
- <sup>6.</sup> 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).
- <sup>7.</sup> 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.
- <sup>8.</sup> 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.
- <sup>9.</sup> Lower GI (LGI) endoscopy (proctoscopy or colonoscopy) will be done on all randomized subjects that have an intact colon or rectum/pouch.
- <sup>10.</sup> 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.
- <sup>11.</sup> On-study Upper GI (UGI) endoscopy will be done on all randomized subjects that have a duodenum.
- <sup>12.</sup> Monthly ( $\pm$  7 days) phone/email contact by the study coordinator to follow-up on medication/drug compliance review, concomitant medications, and adverse events.
- <sup>13.</sup> 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.
- <sup>14.</sup> A food frequency recall questionnaire will be administered at month 36 and 48/EOT visit. US and Canada sites only.
- <sup>15.</sup> A random urine sample (15 mL minimum) will be collected at months 24, 30, 36, 42 and 48/EOT visits for polyamine analysis.
- <sup>16.</sup> 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.
- <sup>17.</sup> EOT visit will occur within 2 weeks off study treatment for any cause including completion of treatment at 48 months.
- <sup>18.</sup> Subject needs to be in the supine position for 10 minutes prior to the EKG.
- <sup>19.</sup> 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.
- <sup>20.</sup> Urinalysis panel includes – color, clarity/appearance, specific gravity, pH, protein, glucose, ketones and blood.
- <sup>21.</sup> 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<sup>1</sup>**

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

<sup>1</sup>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 ( $\pm 2$  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 ( $\pm 1$  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 ( $\pm 2$  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 ( $\pm 1$  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 ( $\pm 1$  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 ( $\pm 2$  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 ( $\pm 2$  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  $\geq 10$  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,  $\geq$  grade 3
- Tinnitus  $\geq$  grade 2, or clinical hearing impairment  $\geq$  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  $\geq$  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  $\geq 3$  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  $\pm 1$  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
	<i>EKG – Prior to pre-dose sample collection and drug administration</i>		
1	Pre-dose*	NA	NA
2	1 hour post dose	45 minutes	75 minutes
3	2 hours post dose	90 minutes	150 minutes
	<i>EKG – Prior to 4 hour sample collection</i>		
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  $\pm 15$  minutes,  $\pm 30$  minutes,  $\pm 60$  minutes (1 hour),  $\pm 120$  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<sup>70</sup> 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<sup>71</sup> 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.<sup>72,73</sup> It provides a simple descriptive profile and a single index value for health status.
- The Cancer Worry Scale<sup>74</sup> 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.<sup>72,73</sup> 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.*<sup>74</sup>

## **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.<sup>82,83</sup> Data from the FFQ will be analyzed using a polyamine database<sup>69</sup> 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<sup>84</sup> 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*<sup>40</sup> 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](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, Health 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<sup>®</sup>, Eliquis<sup>®</sup>, Plavix<sup>®</sup> and other direct thrombin inhibitors), fluconazole, lithium, furosemide and thiazides, DMSO, methotrexate, probenecid, propoxyphene hydrochloride, Tylenol<sup>®</sup> (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.<sup>85</sup> 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<sup>86</sup>. 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<sup>88,89</sup>. 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).<sup>90</sup> 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,<sup>91</sup> 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<sup>92</sup>.

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.<sup>90</sup>

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.<sup>72,73</sup> 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*<sup>74</sup>.

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.<sup>82,83</sup> Data from the FFQ will be analyzed using a polyamine database<sup>69</sup> 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](http://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
°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, difluoromethylornithine
CRC	colorectal cancer
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
dB	Decibels
DFMO	Eflornithine, CPP-1X, difluoromethylornithine
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 polyethylene
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 <sub>1/2</sub>	Half-life
WBC	White Blood Cell
WHO	World Health Organization

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## APPENDIX A SPIGELMAN'S SCORE AND STAGE

### Modified Spigelman's Score and Classification (Saurin, 2004)<sup>93</sup>

	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 cribriformed 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)<sup>94</sup>

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 <ul style="list-style-type: none"> <li>4.1 High grade adenoma/dysplasia</li> <li>4.2 Non-invasive carcinoma (carcinoma in situ)<sup>a</sup></li> <li>4.3 Suspicion of invasive carcinoma</li> </ul>
Category 5	Invasive neoplasia <ul style="list-style-type: none"> <li>5.1 Intramucosal carcinoma<sup>b</sup></li> <li>5.2 Submucosal carcinoma or beyond</li> </ul>

<sup>a</sup> Non-invasive indicated absence of evident invasion.

<sup>b</sup> Intramucosal indicated invasion into the lamina propria or muscularis mucosae.

## APPENDIX B InSiGHT RECTUM/POUCH ASSESSMENT AND STAGE<sup>95</sup>

Stage	Polyp Description	Recommended Intervention	Comment
<b>0</b>	0-10 polyps, all <5mm	Repeat FS in 1 years	
<b>1</b>	10-25 polyps most <5mm, none >1cm	Ablate polyps; repeat sigmoidoscopy in 1 year	Chemopreventive may be considered
<b>2</b>	10-25 polyps, any >1cm, amenable to complete removal	Repeat sigmoidoscopy 6 months Polypectomy preferred	Removal of large polyps clearly necessary  Chemopreventive valuable
<b>3</b>	> 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
<b>4</b>	>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.

<b>Class</b>	<b>Patient Symptoms</b>
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<sup>9</sup>

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

## 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
<ul style="list-style-type: none"> <li>Bertagnolli, et al., N Eng J Med, 2006</li> <li>Bulow, et al., Dis Colon Rectum, 2008</li> <li>Church, et al., Surg Onc Clin N Am, 2009</li> <li>Church, et al., Dis colon Rectum, 2005</li> <li>Groves, et al., Dis Colon Rectum, 2005</li> <li>Huang, et al., Church, Familial Cancer, 2011</li> <li>Nieuwenhuis, et al., Dis Colon Rectum, 2009</li> <li>Tonelli, et al., J Surg Onc, 2000</li> <li>Vasen, The Lancet, 1996</li> <li>West, et al., Gut, 2010</li> </ul>	<ul style="list-style-type: none"> <li>80% of patients develop adenomas within the pouch body.</li> <li>71% ↓ of adenomas after 4-6 mo. Sulindac (300-400mg/day)-analysis combined randomized studies.</li> <li>Incidence of pouch adenomas is time-dependent with 42% of patients at 7 yrs from pouch construction.</li> <li>Median time from pouch construction to diagnosis pouch adenomas, 4.7 yrs (0.5-12 yrs).</li> <li>Celecoxib treated patients, median time to first polypectomy post IRA was 18.69 months; 90.9% (30 patients) had a post IRA rectal polypectomy.</li> <li>Celecoxib treated patients, post IPAA, 3 of 24 pts (12.5%) had post IPAA polypectomy, 21 censored. 25<sup>th</sup> and 50<sup>th</sup> percentiles of time to first polypectomy in IPAA patients was 169.9 months</li> </ul>	<ul style="list-style-type: none"> <li>80% of patients develop adenomas within the pouch body.</li> <li>Celecoxib treated patients, median time to first polypectomy post IRA was 18.69 months; 90.9% (30 patients) had a post IRA rectal polypectomy.</li> </ul> <div> <b>Summary Projected 2 year Event Rate: Excisional intervention and/or high risk adenoma – 40-60%</b> </div>
Duodenal Disease		
Key References	Comments	Event/Rate
<ul style="list-style-type: none"> <li>Recurrence rate of adenoma development is ≥ 50% after endoscopic treatment and treatment is associated with 17% complication rate (perforation, hemorrhage, pancreatitis)</li> <li>Rate of progression between Spigelman stages variable, 4 – 11 yrs</li> </ul>	<ul style="list-style-type: none"> <li>95-100% of all FAP patients develop duodenal adenomas</li> <li>10-25% of patients have Stage III/IV</li> <li>36% of Spigelman Stg IV develop cancer</li> <li>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%.</li> <li>Patients down staged from Spigelman stage IV demonstrate increased rate of disease progression back to severe disease.</li> </ul>	<div> <b>Summary Projected 2 Year Event Rate: Excisional intervention, cancer – 50%</b> </div>
Pre-Colectomy		
	Comments	Event/Rate
	<ul style="list-style-type: none"> <li>Diagnosis with recommendation to proceed with prophylactic colectomy or proctocolectomy.</li> </ul>	<div> <b>Summary Projected 2 Year Event Rate: Excisional intervention, cancer – 90%</b> </div>

**Study ID: CPP FAP-310**

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List of Changes for Protocol Amendment

From Version 2.0, 16April2013 to Version 2.1, 10June2013

Location	Change	Reason for Change
Global Change	<b>Change</b> Version 2.0, 16April2013 <b>To:</b> Version 2.1, 10June2013	Update protocol version and date
<b>Sec. 1.2</b>	<b>Added:</b> SAE reporting to occur through the electronic data capture system or via paper CRF submission. Ockham Drug Safety contact information: Phone: 1-919-462-8867 (US/Canada); 001-919-462-8867 (EU) Fax: 1-919-468-2288 (US/Canada); 001-919-468-2288 (EU)	Update to SAE reporting contact information
<b>Sec. 8.1.3</b>	<b>Deleted:</b> Participant treatment will be unblinded only if the study physician demonstrates a compelling medical need for this information. Specifically, we expect that unblinding of an individual study subject's treatment assignment may occur if in the opinion of the Investigator, and the Medical Monitor, identification of the study medication is necessary to protect the welfare of the subject. The study Medical Monitor must approve the request verbally and later in writing prior to unblinding to ensure that reasons for the unblinding are adequate. The Medical Monitor is a Sponsor representative who has medical authority for the evaluation of the safety aspects of the clinical trial. The study drug may be discontinued without unblinding the participant. <b>Added:</b> 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 of 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 Ockham should be contacted at 1-919-468-2288 (US) and 001-919-468-2288 (EU) for a subject's treatment code.	EU Regulations Requirement
<b>Sec. 11.5</b> <b>5<sup>th</sup> para, 1<sup>st</sup> sentence</b>	<b>Added:</b> "For the FDA, ....	Administrative clarification
<b>Sec. 11.5</b> <b>6<sup>th</sup> para,</b>	<b>Added:</b> For the EU, Reference Safety Information (RSI) is located in the IB (Ver. CPP-201-IB05 and subsequent versions), Section 7.3, page 73, which is to be used for the purposes of determining expectedness and SAE/SUSAR reporting.	EU Regulations Requirement
<b>Sec. 15.</b>	<b>Added:</b> RSI - Reference Safety Information	Administrative clarification
<b>End</b>		

## Study ID: CPP FAP-310

### 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)

#### List of Changes for Protocol Amendment

From Version, 2.0, 16April2013 to Version 2.1, 10June2013 to Version 3.0, 29May2014

Location	Change	Reason for Change
Global Change	<b>Change</b> Version 2.1, 10June2013 <b>To:</b> Version 3.0, 29May2014	Update protocol version and date
Cover/Title Page	<b>Added:</b> to include the EudraCT Number 2012-000427-41 and NCT number 01483144 Updated Version and Date Ver. 3.0, 29May2014 Combined cover page and title page as one.	Admin. clarification
Sec. 1.2	<b>Added: Legal Representative EU</b> Andrew B. Hadlington, Wessex Pharma Services Ltd 19 Webster Road, Winchester, Hants SO22 5NT Phone/Fax: +44 1962 843331 Mobile: +44 7796 394475	Admin. clarification
Sec. 1.5	<b>Deleted</b> Sue Clark and Professor Robin Phillips as Study Co-Principal Investigators <b>Added:</b> Prof. Möslin to study leadership <b>Deleted</b> Ernest Hawk and Miguel as Investigators (MD Anderson Cancer Center <b>Deleted</b> Sue Clark and Professor Robin Phillips as Clinical Site <b>Replaced</b> Randall Burt with Jewel Samadder as PI – Huntsman Cancer Institute. <b>Added:</b> Prof. Sir John Burn, Dr. Alex Henderson as Clinical Site – UK <b>Added:</b> “Prof” to title of Evelien Dekker-NE <b>Change:</b> Malties to “Malalties” <b>Added:</b> Prof. Med. Christian Strassburg and Dr. Robert Hüneburg and University of Bonn, <b>Deleted</b> St. Joseph’s Bochum	Update to reflect current investigator list
Sec. 2.2.1, 2 <sup>nd</sup> para	<b>Inserted:</b> “treatment was”, to read as follows: Benefit was demonstrated in the rectum, but treatment was not statistically beneficial in the duodenum. <b>Corrected typo:</b> urticaria	Admin. clarification
2.4	<b>Revised first sentence as follows:</b> Ornithine decarboxylase (ODC) is a transcriptional target of the MYC oncoprotein....	Admin. clarification
Sec. 2.7.1	<b>Deleted</b> Furthermore, they have implications for this FAP trial, and will affect eligibility (all patients with baseline high cardiovascular risk scores are not eligible for enrollment)	Revised based on cardiovascular criteria
Sec. 5.1.1	<b>Added:</b> ....trial setting in the US “and EU”. The formulation.....	Admin. clarification
Sec. 5.2	<b>Added:</b> 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. <b>Changed:</b> The tablets.... to The sulindac tablets.....	Provides additional information on the use of sulindac in the U.S.
Sec. 6.1, #3.	<b>Deleted</b> ...., except for clinical polyposis....	Admin. clarification
Sec. 6.1., #4a	<b>Added to Stage 3:</b> .....or any “prior” evidence.....	Admin. clarification
Sec. 6.1 # 11		
Sec. 6.1 #11	<b>Added</b> Confirmation of postmenopausal status unless surgically sterile**. **Postmenopausal status may be confirmed by any of the following: a) $\geq$ 12 months spontaneous amenorrhea; b) 6 months spontaneous amenorrhea with serum FSA levels > 30 IU/L [Pagana KD, Pagana	Clarification on how to determine postmenopausal status

Location	Change	Reason for Change
	TJ (2010). <u>Mosby's Manual of Diagnostic and Laboratory Tests</u> , 4th ed. St. Louis: Mosby Elsevier. and Kahwati LC, 54 Nov 2005, The Journal of Family Practice]; c) $\geq 6$ weeks postsurgical bilateral oophorectomy; d) $\geq 6$ weeks postsurgical hysterectomy. <b>footnote * added:</b> "Fertile male or female, effective....."	
Sec. 6.1 #11	<b>footnote changed from:</b> ... should use condoms for the duration of the study and for at least 2 weeks afterwards. <b>To:</b> ... should use condoms 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.	Admin. clarification
Sec. 6.1, #16	<b>Changed:</b> use of 81 mg to "81 to 100 mg" daily of aspirin.... Or "650" to "up to 700"....	European standard of care for prophylactic aspirin use is 100 mg.
Sec. 6.1, # 19	<b>Added:</b> "written"...	Admin. clarification
Sec. 6.2, #2	<b>Added:</b> ...."oral"....	Admin. clarification
Sec. 6.2, #5	<b>Changed:</b> 650 to 700	Update total based on European standard size for low dose aspirin
Sec 6.2, #8	<b>Changed from:</b> Patients at high cardiovascular disease risk are <u>not eligible</u> for study participation as defined below. "High risk" for cardiovascular disease is defined as: <ul style="list-style-type: none"> <li>Clinical diabetes mellitus (Type I or II) requiring glycemic medications, or</li> <li>Prior personal history of cardiovascular disease – heart attack, stroke, transient ischemic attack, or symptomatic peripheral vascular disease, or two of the following: <ul style="list-style-type: none"> <li>Taking anti-hypertensive medication</li> <li>Taking lipid lowering medication <ul style="list-style-type: none"> <li>Current cigarette smoker</li> </ul> </li> </ul> </li> </ul> <b>To:</b> Patients must not have cardiovascular disease risk factors as defined below. <ul style="list-style-type: none"> <li>Uncontrolled high blood pressure (systolic blood pressure &gt; 150 mm Hg;</li> <li>Unstable angina;</li> <li>History of documented myocardial infarction or cerebrovascular accident;</li> <li>New York Heart Association Class III or IV heart failure (Refer to Appendix C);</li> <li>Known uncontrolled hyperlipidemia defined as LDL-C <math>\geq 190</math> mg/dL or triglycerides <math>\geq 500</math> mg/dL.</li> </ul>	Updates cardiovascular criteria for entry. See cover letter for submission for details on this change.
Sec 6.2, #12	<b>Changed:</b> Appendix C to "D"	Admin. clarification
Sec. 8.1	<b>Changed:</b> Mo 1-2 to Mo 0-1-2 <b>Added</b> for clarification a column for month 9, 15 and 21 to note that a serum pregnancy test is to be done in WOCBP <b>Added to footnote 2:</b> CBC "panel includes" <b>Added to footnote #5:</b> "... (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)..." <b>Added to footnote 6:</b> (250, 500, 1000, 2000, 4000 and 8000 Hz) <b>Added to footnote 15:</b> US and Canada sites only	Provides additional detail on what is required for tests and procedures

Location	Change	Reason for Change
	<p><b>Changed footnote # 18:</b> 12 to 6.</p> <p><b>Added to footnote 22:</b> “2” EKGs will “done” .... “after pre-dose sample but prior to dose”, and ...</p> <p><b>Added footnote # 23:</b> <sup>23</sup>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.</p> <p><b>Added footnote # 24:</b> <sup>24</sup>Urinalysis panel includes – color, clarity/appearance, specific gravity, pH, protein, glucose, ketones and blood.</p>	
Sec.8.2.2	<b>Added to paragraph 4:</b> review of body systems,	Clarifies what will be done during the physical exam
Sec. 8.2.5	<p><b>Added to month 3:</b> .... (after the pre-dose sample, but prior to drug administration....)</p> <p><b>Added to months 3, 6, 12, and 18:</b> review of body systems,</p> <p><b>Added:</b> At the 9 month visit patients 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.</p> <p><b>Added:</b> At the 15 month visit patients 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.</p> <p><b>Added:</b> At the 21 month visit patients 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.</p> <p><b>Added to paragraphs for months 6, 12 and 18:</b> “Concomitant medications, adverse events and medication compliance will also be reviewed”.</p>	Clarifies the timing for the EKG
Sec. 8.2.6	<p><b>Added to first paragraph:</b> Concomitant medications, adverse events and medication compliance will also be reviewed.</p> <p><b>Added:</b> review of body systems,</p>	Updates the information to be collected during the visit
Sec. 8.2.7	<b>Added to first paragraph:</b> Concomitant medications and adverse events will also be reviewed.	Admin. clarification
Sec. 8.2.9	<b>Added:</b> Discontinuation from study treatment .... Grade $\geq 3$ Cardiac ischemia/infarction or cerebrovascular ischemia, whether related to study drug or not	Updated safety monitoring based on revised cardiovascular criteria
Sec. 8.3.1	<b>Changed:</b> changed “of” to “to”	Admin. clarification
Sec. 8.3.2	<b>Added:</b> #3. Grade $\geq 3$ cardiac ischemia/infarction or cerebrovascular ischemia, whether related to study drug or not.	Updated safety monitoring based on revised cardiovascular criteria
Sec. 8.3.2	<p><b>Changed:</b> re-arranged all numbers after number 3</p> <p><b>Added to # 7:</b> ...”(randomization date)” and ...”of”</p>	Admin. clarification
Sec.9.1.A	<p><b>Added:</b> All rectal/pouch polyps &gt; 5 mm in diameter must be excised at baseline if the subject will be stratified to the rectum/pouch group. For details concerning patients stratified to the rectal/pouch polyposis group (with or without involvement of the duodenum) please see</p>	Clarifies when >5 mm polyps need to be removed from the rectum/pouch based on the stratification

Location	Change	Reason for Change
	Section 6.1.4. For details concerning patients stratified to the duodenal polypoid group (with or without involvement of rectum/pouch at stratification) please see Section 8.2.9.	group for the subject.
Sec. 9.4	<b>Added in 3<sup>rd</sup> paragraph:</b> ...will be collected and “ <b>after this, a</b> ” pre-dose ... Patients will be asked to note the time breakfast was finished, as that will be recorded.	Admin. clarification
Sec. 9.4	<b>Change to table 5 footnote:</b> ... pre-dose “sample but before drug administration” and “after the” 4...	Admin. clarification
Sec. 9.4	<b>Changed in 4<sup>th</sup> paragraph:</b> third and fourth samples <b>to:</b> fourth and fifth samples	Admin. clarification so table matches text
Sec. 11.1	<b>Change from:</b> Only subjects meeting the inclusion criteria will be enrolled in the study. <b>To:</b> Subjects with cardiovascular risk factors as defined in Section 6.2 are not eligible for study participation.	Updates eligibility status based on cardiovascular risk factors.
Sec. 13.7	<b>4<sup>th</sup> sentence, Added:</b> “minimum”	Admin. clarification
Sec. 15	<b>Added:</b> HEENT-Head, Ears, Eyes Nose Throat, and EU-Europe	Added abbreviations used in text
Sec. 16	<b>Added Reference</b> #75 Pagana KD, Pagana TJ (2010). <u>Mosby’s Manual of Diagnostic and Laboratory Tests</u> , 4th ed. St. Louis: Mosby Elsevier. #76 Kahwati LC, Haigler, L, Rideout S. What is the best way to diagnose menopause?. The Journal of Family Practice 54:11: 1000-1002, 2005. <b>Reference numbers updated</b>	Update references for additional information on postmenopausal status.
Appendix C	<b>Added:</b> Appendix C, New York Heart Association Classification Table	Provides information on NYHA classification that is now a part of eligibility criteria.
End		

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**List of Changes for Protocol Amendment**

From Version 3.0, 29May2014 to Version 3.1, 20March2015

Location	Change	Reason for Change
Global Change	<b>Change</b> Version 3.0, 29May2014 <b>To:</b> Version 3.1, 20March2015	Update protocol version and date
Table of Contents	Update Table of Contents to reflect changes.	
Section 1.3	<b>Change:</b> University of Arizona, BIO5 Institute Oro Valley and Arizona Cancer Center in Tucson, Arizona will perform the polyamine, pharmacogenomics and genetics testing for the samples collected. <b>To:</b> Metabolon Inc., 617 Davis Drive, Ste. 400, Durham NC, 27713, USA, will perform the testing for the polyamine samples collected.  Molecular MD Inc. 1341 SW Custer Drive, Portland OR, 97219, USA, will perform the testing for the pharmacogenomic samples collected  inVentiv Health Clinique, Inc. rue Einstein Street, Québec City, Québec G1P 0A2, Canada, will perform the bioanalysis for the pharmacokinetic samples collected.	Update to reflect current bioanalytical labs
Section 1.5	<b>Added Investigators</b> <b>Prof. Dr. Med Christian Strassburg</b> <b>Robert Hüenbun, M.D.</b> Department of Hepato-Gastroenterology University of Bonn Hospital, Bldg. 334, 2 <sup>nd</sup> floor Sigmund Freud Str 25 Bonn, Germany 53127 <b>Anil Rustgi, M.D.</b> University of Pennsylvania Perelman School of Medicine 3400 Civic Center Blvd, 4 S Pavilion Philadelphia PA, 19104 USA <b>Samir Gupta, M.D.</b> University of California San Diego Dept. of Gastroenterology, Moores Cancer Center 3855 Health Sciences Dr. La Jolla CA, 92093 USA <b>Fiona Laloo, M.D.</b> Manchester Centre For Genomic Medicine Central Manchester University Saint Mary's Hospital- Oxford Road Manchester M13 9WL, UK <b>Giovanna da Silva, M.D.</b> Cleveland Clinic Florida 2950 Cleveland Clinic Blvd. Weston FL, 33331 USA <b>Professor Eric Van Cutsem, M.D., Ph.D.</b> Leuven Cancer Institute	Update to reflect current investigator list

Location	Change	Reason for Change
	<p>University Hospitals Leuven 3000 Leuven, Belgium <b>Dr. Jennifer Weiss, M.D.</b> University of Wisconsin-Madison Division of Gastroenterology and Hepatology UWM Centennial Building 1686 Highland Avenue Madison, WI 53792 USA <b>William Grady, M.D.</b> Fred Hutchinson Cancer Research Center/University of Washington/ 1100 Fairview Avenue N. D4-100 Seattle, WA 98109 USA <b>Douglas Riegert-Johnson, M.D.</b> Mayo Clinic-Florida 4500 San Pablo Road Jacksonville, FL 32224 USA</p>	
Section 4.4	<b>Clarification:</b> ...includes progression to more advanced duodenal polyposis (Stage 2, 3 or 4),	
Section 4.8	<b>Changed:</b> "...oligonucleotide primers designed to amplify a 172-bp fragment containing the polymorphic base at +316 (Applied Biosystems). Allele-specific TaqMan probes will be synthesized with different 5' labels (6-carboxyfluorescein or VIC) and the same 3' quencher dye (6-carboxytetramethylrhodamine). Each PCR reaction (5 µL total) will contain 10 ng of participant DNA, 30 pmol of each primer, 12.5 pmol of each TaqMan probe, and 1× TaqMan Universal PCR Master Mix (Applied Biosystems)." <b>To:</b> ... 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.	Administrative
Section 6.1	<b>#17 Added after aspirin,</b> "in excess of 700 mg weekly, <b>#18 Added:</b> "oral" before corticosteroids	
Section 6.2	<b>#6: Added at the end of the sentence "and or randomization."</b> <b>#10, Change:</b> Colon/rectum/pouch with high grade dysplasia or cancer on biopsy or a large polyp (>1 cm) not amenable to complete removal. <b>To:</b> 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.	Administrative
Section 8.1	<b>#5, Change:</b> Complete Physical Exam (includes body system assessment/review of systems - ... <b>To:</b> Physical Exam/Review of body systems (includes body system assessment - ... <b>#10 Added:</b> ... that have an intact colon or rectum/pouch. ... <b>#11 Added:</b> ... For patients with permanent ileostomy, endoscopy not required; normal mucosal biopsies are performed on the visible ileostomy stoma.	Administrative

Location	Change	Reason for Change
	<b>#12 Added:</b> ... that have a duodenum.	
Section 8.1	<p><b>#22 New number:</b> Subject needs to be in the supine position for 10 minutes prior to the EKG.</p> <p><b>#22 changed # to 23:</b> 2-EKGs will done on the day PK samples are collected: after pre-dose sample but prior to dose, and after the 4 hr PK sample has been obtained.</p> <p><b>To:</b> 2-EKGs will 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.</p> <p><b>Updated:</b> #23 to 24 and 24 to 25</p>	Administrative
Section 8.2.2	<p><b>Lower GI, Changed:</b> All randomized patients will have baseline ...</p> <p><b>To:</b> All randomized patients with an intact colon or rectum/pouch will have baseline ...</p> <p><b>Upper GI Change:</b> All randomized patients will have baseline and on-study UGI endoscopy as part of this trial. A complete physical exam including review of body systems, ...Baseline blood tests within ...</p> <p><b>To:</b> 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 a 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, ...</p> <p>Baseline blood and urine tests within ...</p>	Administrative
Section 8.2.5	<p><b>Change:</b> At the 3-month visit, patients will have a physical exam ...</p> <p><b>To:</b> At the 3-month visit, patients will have a physical exam/review of body systems ...</p> <p><b>Added:</b> At the 6-month .... Review or “body” systems</p> <p><b>Changed:</b> At the 12 month visit patients will have a physical exam (including review of body systems, weight and vital signs) ...</p> <p><b>To:</b> At the 12 month visit patients will have a physical exam/review of body systems (including, weight and vital signs).</p> <p><b>Changed:</b> At the 18 month visit patients will have a physical exam (including review of body systems, weight and vital signs) <b>To:</b> At the 18 month visit patients will have a physical exam/review of body systems (including, weight and vital signs)..</p> <p><b>Changed:</b> At the 3-month visit ... (PK), and EKGs (after the pre-dose sample, but prior to drug administration and after the 4-hour PK sample collection). <b>To:</b> ... (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 prone or lying down position for 10 minutes prior to collecting the EKG).</p> <p><b>Added to Month 6, 12, and 18:</b> (Subject needs to be in the supine position for 10 minutes prior to the EKG).</p>	Administrative
Section 8.2.6	<p><b>Added:</b> (Subject needs to be in the supine position for 10 minutes prior to the EKG)</p> <p><b>Changed:</b> ... physical exam (including review of body systems, weight</p> <p><b>To:</b> ... physical exam/review of body systems (including, weight ...</p>	Administrative
Section 8.2.9	<b>Added to 3. a)....(Stage 2, 3 or 4)</b>	Administrative
Section 9.2	<b>Added:</b> after.. Spigelman stage progression “ (Stage 2, 3, 4)”	Administrative
Section 9.4	<b>Changed:</b> Thereafter, a pre-dose blood sample (5 mL, lithium heparin vacutainer tube) will be collected and after this, a pre-dose EKG will be	Administrative

Location	Change	Reason for Change
	<p>obtained. <b>To:</b> <u>Prior to the pre-dose blood sample collection</u>, a resting EKG will be obtained (patient needs to be in the supine position for 10 minutes prior to collecting the EKG). <u>After the EKG was obtained</u>, a pre-dose blood sample (5 mL, lithium heparin vacutainer tube) will be collected.</p> <p><b>Table 5: added EKG – Prior to pre-dose sample collection and drug administration and EKG – Prior to 4 hour sample collection</b></p> <p><b>Table footer changed from:</b> *EKGs need to be done after the pre-dose sample but before drug administration and after the 4 hour samples have been collected.</p> <p><b>To:</b> *EKGs need to be done <b>1) before</b> the pre-dose sample and before drug administration and <b>2) before</b> the 4 hour samples are collected.</p> <p><b>Added:</b> At the 4 hour time point and <u>prior to the 4 hour blood sample collection</u>, 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.</p>	
Section 11.7	<b>Added:</b> physical examination"/review of body systems".	Administrative c
Section 11.9	<p><b>Added before corticosteroids “oral”</b></p> <p><b>Added</b> after aspirin “in excess of 700 mg weekly,”</p> <p><b>Changed:</b> ... Pradaxa®, and Plavix®) or other direct thrombin inhibitors), fluconazole...<b>To:</b> ... Pradaxa®, Eliquis®, and other direct thrombin inhibitors, and Plavix®) fluconazole...</p>	Administrative
Appendix A	<p><b>Added comment:</b></p> <p>All adenomas in the duodenum demonstrate at least low grade dysplasia; if intermediate grade use low grade for points.</p>	Administrative
<b>End</b>		

**Study ID: CPP FAP-310**

**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)**

**List of Changes for Protocol Amendment**

From Version 3.1, 20March2015 to Version 3.1a, 23July2015

Location	Change	Reason for Change
Global Change	Change Version 3.1, 20March2015 To: Version 3.1a, 23July2015	Update protocol version and date
Section 1.6	Changed: SCHEMa to SCHEMA	Administrative
Reference number citations and measurements	Formatted updated as superscript numbers.	Administrative
Section 8.1, Table 3	Formatted footnotes as superscript in table and listing of footnotes	Administrative
Appendices, Appendix E	Formatted tables to fit on 1 page	Administrative
Protocol synopsis	Version change for consistency with protocol version and date. No changes were made to the synopsis document.	Administrative
<b>End</b>		

**Study ID: CPP FAP-310 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)**

**List of Changes for Protocol Amendment**

From Version 3.1a, 23July2015 to Version 4.0, 14March2016

Location	Change	Reason for Change
Global Change	<b>Changed:</b> Version 3.1a, 23July2015 <b>To:</b> Version 4.0, 14March2016	Update protocol version and date
Global Changes	Corrected typographical and grammatical errors Updated cross reference Sections throughout the document	Administrative changes
Section 1.2	<b>Added</b> additional information on Legal Representative Cancer Prevent Pharma, Ltd Tower 42, Level 30 International Finance Center 25 London, EC2N 1HQ, United Kingdom <b>Changed:</b> Ockham Drug Safety contact to Chiltern Drug Safety Contact, <b>Added:</b> Email: dsafety@chiltern.com	Administrative change
Section 1.5	Added: contact information for Dr. Willingham and Dr. Cone and deleted information for Dr. Rigert Johnson.	Update to participating sites
Section 1.6	<b>Changed:</b> For enrolled subjects treatment will continue for 24 months, or until occurrence of an FAP-related event as defined in the protocol. Drugs taken once daily. <b>To:</b> 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 event can continue treatment for up to 12 additional months until one of the following occurs: 1) subject has an FAP event or comes off study for other reasons, 2) all randomized subjects have reached a minimum of 24 months of treatment or have come off study prior to reaching 24 months of treatment.	Adds information on treatment extension for up to a maximum of 12 additional months of treatment.
	<b>Move:</b> "Drugs taken once daily" <b>after</b> "a total of 150 patients"	Administrative change
Section 2.2.3	<b>Remove:</b> "Dr. Patrick Lynch, the study Principal Investigator, reported results from this trial in abstract form at the 2012 Digestive Diseases Week (DDW) meeting in San Diego and the 2012 Collaborative Group of the Americas for Inherited Colorectal Cancer in Boston."	Updated with published ref. instead of meeting abstract.
Section 2.3	<b>Added:</b> ...patients treated <b>for three (3)</b> years with eflornithine...	Clarification on duration of study treatment in referenced study.
Section 2.2.4	<b>Deleted:</b> "2012", Added publication reference.	Administrative change
Section 2.7.3	<b>Added:</b> "and the recent FDA Drug Safety Communication", and reference	Adds reference to FDA Safety letter for sulindac.
Section 3.2 Rationale for Treatment Duration Extension	Added a new section 3.2 on Rationale for Treatment Duration Extension. See attached section at the end of this document.	Provides the rationale and data for treatment duration extension.

Location	Change	Reason for Change
Section 3.2: Purpose ( <b>now Section 3.3</b> )	<b>Changed:</b> 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 <b>single agents over a 24 month treatment</b> period in patients with Familial Adenomatous Polyposis (FAP). <b>To:</b> single agents <b>with up to a 36 month maximum</b> treatment...	Changes maximum treatment duration for treatment extension.
Section 4.2	Bullet point #3 changed <b>24 months</b> to <b>36 months</b> . Added last 2 bullet points on initial 24 months of treatment and treatment extension: <ul style="list-style-type: none"> <li>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).</li> <li>Subjects completing 24 months of treatment without an FAP event can continue treatment for up to 12 additional months until one of the following occurs: 1) subject has an FAP event or comes off study for other reasons, 2) all randomized subjects have reached a minimum of 24 months of treatment or have come off study prior to reaching 24 months of treatment.</li> </ul>	Changes maximum treatment duration and adds information on initial treatment and treatment extension.
Section 4.7	<b>Changed on first paragraph:</b> At the scheduled colonoscopy/proctoscopy at baseline, 6 months and 24 months... <b>To:</b> “At each colonoscopy/proctoscopy while on study treatment, a sample of normal rectal mucosa and a random urine sample will be obtained to assess .....”	Clarifies time point sample collection and adds time points for treatment extension.
Section 5.1	<b>Changed</b> “patients” <b>To</b> “subjects”	Administrative change
Section 5.2	<b>Changed</b> “patients” <b>To</b> “subjects”	Administrative change
Section 8.1	<b>Added to the title:</b> Table 3 ... ( <b>Initial 24 months of treatment</b> ). And added to month 24 “X <sup>26</sup> ” for Informed consent <b>Added to footnotes:</b> <sup>26</sup> 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.	The table has been divided into the initial 24 months of treatment (Table 3) and Table 4 for treatment extension up to 36 months.
Section 8.1	<b>Added:</b> New table # 4 and table 4 footnotes. See complete table and footnotes at the end of this document.	Explains treatment extension procedures
Section 8.2.4	<b>Changed:</b> Table 4 to table 5. <b>Changed:</b> On RX intervals “daily for 24 months” <b>To:</b> Daily for <b>up to 36 months</b> ” <b>Changed:</b> Based on published data utilized to project event rates, patients will receive treatment for <b>24 months</b> . <b>To:</b> Based on published data utilized to project event rates, patients will receive treatment for <b>up to 36 months</b> .	Administrative change Changes maximum treatment duration.
Section 8.2.5	<b>Changed Section Heading:</b> Follow-up During Treatment Intervention. <b>To:</b> <b>Initial 24 Month Treatment Intervention Assessments</b> .	Changes maximum treatment duration and adds

Location	Change	Reason for Change
	<p><b>Changed:</b> Refer to Section 8.1, <b>Table 3</b> for patient assessments and the treatment schedule for screening, on-study, end of treatment and follow-up visits.</p> <p><b>To:</b> Refer to Section 8.1, Table 3 and Table 4 for patient assessments and the treatment schedule for screening, on-study, end of treatment and follow-up visits.</p> <p><b>Added:</b> During the <b>initial</b> 24 month drug intervention, patients will be followed monthly by phone interview <b>or in person visits</b> for assessment ...</p>	information on initial treatment and treatment extension.
Section 8.2.5	<p><b>Added paragraph:</b> At months 1, 2, 4, 5, 7, 8, 10, 11, 13, 14, 16, 17, 19, 20, 22, 23 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.</p>	Clarifies monthly phone calls
Section 8.2.5	<p><b>Changed:</b> At the 6-month, visit.... A second normal rectal/pouch mucosal biopsy for polyamine determination.</p> <p><b>To:</b> (CBC, chemistry panel, urinalysis), <b>a random urine sample will be obtained for polyamine determination</b>, ... and their first on study treatment upper and lower endoscopy procedures <b>with image and video documentation will be obtained...</b></p> <p><b>Added:</b> At the month 12 and at the month 18 visit... <b>a random urine sample will be obtained for polyamine determination...</b></p> <p>And: ...endoscopy procedures <b>with image and video documentation will be obtained. A normal mucosal biopsy sample for polyamine determination will be obtained during the colonoscopy/proctoscopy procedure...</b></p>	Clarifies time points for collection and adds time points for treatment extension.
Section 8.2.6 Original split into Section 8.2.6 and 8.2.7	<p><b>Changed section and contents:</b> Final Intervention Visit/End of Treatment (Month 24 +/- 2 weeks or at end of treatment +/- 2 weeks).</p> <p><b>To new section and contents:</b> Month 24 (<math>\pm</math> 2 weeks) and modification of the whole section. See updated section at the end of this document.</p>	Updates month 24 procedures to include treatment extension.
Section 8.2.7	<p><b>Changed section heading to:</b> Follow-Up (30-days post end of treatment visit +/- 1 week) Off Study.</p> <p><b>To:</b> Initial 24 Month Treatment Intervention Early Termination (+ 2 weeks).</p> <p><b>Removed:</b> (with normal mucosa biopsy and random urinalysis for polyamine analysis)</p> <p><b>Added to first paragraph:</b> (CBC, chemistry panel, and urinalysis), <b>a random urine sample will be obtained for polyamine determination...</b></p> <p><b>Added to second paragraph:</b> “A normal mucosal biopsy sample for polyamine determination will be obtained during the colonoscopy/proctoscopy procedure.”</p> <p><b>Added to third paragraph:</b> A random urine sample should be obtained for polyamine determination, if possible.</p>	Clarifies time points sample collection and adds time points for treatment extension.
Section 8.2.7	<p><b>Added:</b> 90 days <b>from randomization...</b></p>	Clarifies when the cumulative delay starts
Section 8.2.8 and 8.2.9	<p><b>Changed section numbers:</b> from 8.2.7 to 8.2.8 and 8.2.8 to 8.2.9</p> <p><b>Added to both titles:</b> “Initial 24 Month Treatment Intervention”</p>	Updates information for initial 24 month treatment.

Location	Change	Reason for Change
Sections 8.2.10-8.2.14	<b>Added new sections and contents:</b> Sections 8.2.10-8.2.13 See sections at end of document.	Clarifies procedures for treatment extension.
Section 8.2.14	<b>Added</b> (~25% increase in disease burden) to the following sentence as follows:  ^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.	Administrative Change
Section 8.3.1	<b>Changed on last paragraph:</b> ...Drug Safety Group at <b>Ockham</b> should... <b>To:</b> ...Drug Safety Group at <b>Chiltern</b> should...	Clarifying change in safety group name.
Section 8.3.2	<b>Moved from # 7:</b> “The first day of study treatment initiation is the randomization date regardless of study visit and/or procedure delays.” and <b>Move to the end of #6.</b> <b>Added to #6:</b> (from randomization) <b>Changed from #7:</b> 24 months <b>To:</b> treatment <b>Corrected numbering for #9-11.</b>	Administrative change
Section 9.5	<b>Changed:</b> ...and at the 6 month and 24 month proctoscopy... <b>To:</b> ...and at <u>each endoscopy</u> /proctoscopy...	Clarifies time points for sample collection and adds time points for treatment extension.
Section 10.1	<b>Changed:</b> HRQoL measures will be obtained at baseline and at 3, 6, 12, 18, and 24 months post-enrollment/end of treatment. <b>To:</b> HRQoL measures will be obtained at baseline, month 3, at every interim endoscopy visit, and at end of treatment <b>Changed:</b> In addition to the HRQoL... Data will be collected at baseline and at 3, 6, 12, 18, and 24 months post-enrollment/end of treatment and preference... <b>To:</b> In addition to the HRQoL... Data will be collected <u>at baseline, month 3, at every interim endoscopy visit, and at end of treatment</u> and preference... <b>Changed:</b> The modified version of the Cancer Worry Scale will also be administered at baseline and at 3, 6, 12, 18, and 24 months <b>To:</b> The modified version of the Cancer Worry Scale will also be administered <u>at baseline, month 3, at every interim endoscopy visit, and at end of treatment</u> and...	Updates time points to include treatment extension.
Section 10.2	<b>Changed:</b> ... Dietary assessments via the FFQ will be obtained at baseline, 12 months and 24 months/end of treatment... <b>To:</b> ... Dietary assessments via the FFQ will be obtained at baseline, <u>months 12, 24 and 36</u> /end of treatment...	Update time points to include treatment extension.
Section 11.1	<b>Changed:</b> ...and months 3, 6, 12, 18 and 24 (end of treatment). <b>To:</b> ...and months 3, 6, 12, 18, 24, 30 and 36/end of treatment.	Update time points to include treatment extension.
Section 11.2 Purpose	<b>Changed:</b> At the 3, 6, 12, 18 and 24 month visits... <b>To:</b> At months 3, 6, 12, 18, 24, 30 and 36/end of treatment...	Update time points to include treatment

Location	Change	Reason for Change
		extension.
Section 11.3	<b>Changed:</b> At the 3, 6, 12, 18 and 24 month visits... <b>To:</b> At months 3, 6, 12, 18, 24, 30 and 36/end of treatment...	Update time points to include treatment extension.
Section 11.5	<b>Spelled out IB</b> – Investigator’s Brochure <b>Removed:</b> page 73	Administrative change
Section 11.8	<b>Added:</b> ...have become pregnant ( <b>for male subjects if their partner has become pregnant</b> ) at the time...	Clarifies reason to report pregnancy
Section 12	<b>Changed:</b> Eligible patients who have given informed consent will enter the study the intent to participate for the full treatment period of 24 months. Accrual is expected to take 6-12 months.  <b>To:</b> Eligible patients who have given informed consent will enter the study with the intent to participate for the full treatment period of 24 months. 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 12 months.	Explains the change in accrual time frame and updates procedures for treatment extension.
Section 12.1	<b>Changed:</b> The analytic method for the primary analysis will be a time-to-event analysis using the log-rank test. <b>To:</b> ... analysis using the <b>stratified</b> log-rank test.  <b>Changed:</b> 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.  <b>To:</b> If the endpoint determination cannot be made at the end of study clinic visit per the pre-specified study requirements, a blinded adjudication committee will review the reasons for such deviations. If upon blinded adjudication it can be determined that a subject’s withdrawal is for reasons deemed unrelated to his or her endpoint status, that subject will be treated as a censored observation as of the last patient visit. If upon blinded adjudication it cannot be determined that a subject’s withdrawal is unrelated to endpoint status, an imputed primary endpoint will be used in the primary analysis for such withdrawals. The time to this imputed event will be from randomization to the last recorded patient visit. All other subjects who complete their follow-up without a FAP-related event by the end of the study will be treated as a censored observation as of the actual follow-up time for the close-out visit.  Prior to the primary analysis, balance will be assessed between the three arms in terms of key potential confounders measured at the baseline visit. A brief list of such potential confounders will be presented to the DMC for approval prior to analysis. 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 the primary analysis using a stratified Cox model including that term in addition to the treatment arm. The covariate-adjusted score test (adjusted stratified log-rank test) will serve as the primary result for the trial.	Updated to match Statistical Analysis Plan.  Clarifies procedures for endpoint determination, matching the information provided in the Statistical Analysis Plan.
Section 12.5.3	<b>Deleted:</b> ...who completed all 24 months of treatment and has primary endpoint determinations performed per protocol specifications. <b>Added:</b> ... that fulfill all protocol eligibility, intervention, and outcome assessments.	Updated to include treatment extension.

Location	Change	Reason for Change
12.5.4	<b>Changed :</b> “Within the entire patient population there will be subsets who did not receive 24 months of daily medication. The patient diary.....” <b>To:</b> “Within the entire patient population there will be subsets who did not receive the full course of per protocol treatment. The patient diary and pill count will define the extent of compliance. This subgroup of patients will be categorized into various cohorts. For consistency, an adjudication committee will be established, to review all study events (i.e., FAP-related events and dropouts) and categorize them either as censored observations or imputed endpoints. For exploratory and sensitivity analysis the following dropout subsets will be included in secondary analyses:”	Clarification on subsets
Section 12.6.1	<b>Added:</b> Demographic features ... <b>and country</b> among ... <b>Added to end of paragraph:</b> 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.	Updated to match Statistical Analysis Plan
Section 12.6.2	<b>Changed:</b> and will include per treatment group enumeration of all patients randomized, number ineligible, early termination due to AE/SAE, the number of subjects with an SAE, deaths, dropout for other reasons, and the number of subjects... <b>To:</b> 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 for more than 90 days, withdrawals of consent for continued follow-up, withdrawals for other reasons, and the number... <b>Changed:</b> Additional summaries will include reasons for patients discontinuing treatment and/or modifying treatment dosages, <b><u>and a summary of patients’ treatment status.</u></b> <b>To:</b> Additional summaries will include reasons for patients discontinuing treatment and/or modifying treatment dosages.	Updates disposition to provide additional detail and match Statistical Analysis Plan.
Section 12.6.3	<b>Added</b> “freedom” to ...one degree of freedom test.. <b>Updated</b> CTCAE version 4 to Version 4.03	Administrative change
Section 12.6.4	<b>Changed:</b> Subgroups will be analyzed in the spirit of exploratory analyses included but not limited to various study populations and within each level of randomization strata. <b>To:</b> 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.	Updated to match the Statistical Analysis Plan for analyzing events.
Section 12.6.5	<b>Changed:</b> ... at baseline and months 3, 6, 12, 18, and 24 months post end of treatment. <b>To:</b> ... at baseline and months 3, 6, 12, 18, 24, 30 and 36/end of treatment.	Updated to include data on treatment extension
Section 12.6.6	<b>Changed:</b> ... at baseline, 12 months and 24 months/end of treatment... <b>To:</b> ... at baseline, months 12, 24 and 36/end of treatment... <b>Deleted:</b> “The results of the FFQ will be used to corroborate results from another recent trial that indicate consumption of a diet high in polyamines is associated with reduced treatment efficacy.”	Updated to include data on treatment extension.
Section 12.7	<b>Added:</b> ... The time to this imputed event will be from randomization to the last recorded patient visit. A study event adjudication committee will be formed to further define the methods for defining imputed and censored	Updated to match the Statistical Analysis Plan for

Location	Change	Reason for Change
	events. <b>Changed:</b> “September 1998” to “February 1998” <b>Added:</b> erroneous <b>or appear as outliers</b> will	analyzing events.
Section 12.8	<p><b>Changed:</b> 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 (based on a blinded A/B comparison). The method for reassessment of sample size is based upon the FDA Guidance, “<i>Adaptive Design Clinical Trials for Drugs and Biologics (February 2010)</i>”. There will be no hypothesis testing. The DMC will perform an assessment of 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 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. With this approach study enrollment can continue uninterrupted at the study sites, if it is decided to increase study sample size.</p> <p>The futility assessment will occur when approximately 50% of maximum trial information has been amassed. Assuming a constant enrollment rate over 1 year and full enrollment achieved at one year, that would occur at approximately 1.5 years from enrollment start. At that time patients would have an average of approximately 1.0 year on study treatment.</p> <p><b>To:</b> 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.</p> <p>The method for reassessment of sample size is based upon the FDA Guidance, “<i>Adaptive Design Clinical Trials for Drugs and Biologics (February 2010)</i>”. 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.</p> <p>The futility assessment will be performed after a total of 45 adjudicated primary endpoints have occurred, which represents 50% of expected maximum trial information, or as soon thereafter as possible. The futility analysis will be performed for each of the two treatment comparisons contained in the primary objective:</p> <ol style="list-style-type: none"> <li>1. CPP-1X active + sulindac active vs. CPP-1X placebo + sulindac active,</li> <li style="text-align: center;">and</li> <li>2. CPP-1X active + sulindac active vs. CPP-1X active + sulindac</li> </ol>	Updates the explanation of the futility analysis to match the Statistical Analysis Plan.

Location	Change	Reason for Change
	<p>placebo</p> <p>For the futility interim analysis, the futility stopping criterion of <math>Z=0.50</math> is one-sided, and corresponds to a conditional power criterion of approximately 0.12 (to two decimals). That is, assuming between 52 and 55 expected total number of events have occurred by trial end in either of the two-arm comparisons, 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, then under the design alternative hazard ratio of 0.4243, there would be only a 12% probability (or less) 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 the trial for futility. The futility analysis results will be presented in a simple manner whereby the DMC will be informed that the conditions indicating futility have been met (i.e. the futility boundary has been crossed, yes or no). Unless the DMC requires it on ethical grounds, no early stopping for positive efficacy is proposed.</p>	
Section Appendix B	<p><b>Added:</b> Patients who cannot be allotted a particular stage (e.g., patients with mix polyposis) contact Cancer Prevention Pharmaceuticals for assistance with staging assignment.</p> <p><b>Deleted:</b> InSiGHT meeting 2011, San Antonio, TX</p>	Updated publication of staging system.
	<b>Added footnote:</b> * Stage I may also include larger, stable, asymptomatic desmoids	Clarification of stage I based on reference publication.
Global	<b>Changed:</b> FAP related event; <b>To:</b> FAP-related event	Administrative change
Global	All section numbers, table numbers, reference numbers, where changed as needed to match the sited number throughout the document. Tables were re-numbered to accommodate to added tables.	Administrative change
<b>End</b>		

## Section 3.2 Rationale for Treatment Duration Extension

At the time of this amendment, the accrual of study subjects was 95% complete. The initial statistical analysis plan used detailed event rate projections based on an extensive review of the published literature (Refer to Appendix E) that determined 150 randomized subjects would be required for the primary endpoint analysis. 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 is unlikely we will reach the required 90 events before the end of the study. In order to reduce the risk of a false-negative trial (because of inadequate events after two years of study treatment in 150 randomized subjects), several mitigation options were explored.

The most effective approach to ensure that the required total number of primary endpoint events is reached is an amendment extending the treatment duration from 24 months up to a maximum of 36 months for subjects that have not had an FAP related event. The study will conclude when the last randomized subject reaches 24 months of treatment. The treatment extension will not increase the overall total trial duration compared to recruiting additional subjects beyond 150 and following them for 24 months.

In order to minimize bias introduced by offering up to an additional 12 months of treatment to patients who have reached 24 months without an FAP-related event, data will be obtained to prospectively define patients who accept or decline the additional months of study treatment. Most importantly, it will be possible to identify the reasons why subjects decline the treatment extension, including real or perceived side effects of the study medications.

To support the treatment extension, a blinded safety review was undertaken. As of February 1, 2016, the CPP FAP-310 study had randomized 140 subjects to one of three treatment arms: (1) eflornithine 750 mg/day, (2) sulindac 150 mg/day, and (3) the combination at the same dosage, with a maximum treatment duration of 24 months. For the ongoing S0820 (PACES, NCT01349881), a study for prevention of recurrence of high risk adenoma and second primary colorectal cancers (managed by SWOG), 67 subjects had been randomized as of November 2015, with a maximum treatment duration of 36 months. In this four arm trial, treatment groups include: (1) eflornithine 500 mg/day, (2) sulindac 150 mg/day, (3) the combination at the same dosage, and (4) placebo/placebo.

Ongoing blinded evaluations of the active Phase III studies has not demonstrated any risks outside of those identified in the Reference Safety Information located in the Investigator's Brochure. There have been no deaths on either study. Safety risks are formally evaluated by a data monitoring committee (DMC) for each study. There have been three safety data monitoring committee meetings for CPP FAP-310 study. To date, the DMC has not identified any safety issues and there have been no 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.

There have been eight (8) serious adverse events (SAEs) that have been reported from the CPP FAP-310 study and five (5) that have been reported from the S0820 study, for a total of 13 serious adverse events. No events were classified as SUSARs and no subject treatment arm assignments were unblinded.

Overall (CPP FAP-310 and S0820 combined), ten (10) of the thirteen (13) SAEs were classified as not related to study treatment by the Investigators. Gastrointestinal events included two (2) small bowel/intestinal obstructions. This type of event is not uncommon in either patient population. There were two (2) gastrointestinal events of ileus, one with diarrhea. The CPP FAP-310 trial patient with ileus had additional episodes prior to taking the study drugs. Ileus is an expected event in the FAP and post colon surgery patient populations. There was one (1) procedural complication that involved a post-polypectomy bleed. This is a common complication from an endoscopic excision. There was one (1) event of pancreatitis in a subject with a prior history of pancreatitis. Pancreatitis is a rare, but identified risk of sulindac. The patient was hospitalized for six weeks and the event was a life-threatening, grade 4 serious adverse event. The Investigator's Brochure,

Sulindac package Insert and published reports indicate that pancreatitis is associated with the use of sulindac.<sup>66</sup> One (1) subject experienced sinusitis with fever and lymphopenia that required hospitalization with IV fluids. There was one (1) event in the nervous system disorders category that was seasonal migraine. The 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. For vascular disorders, there was one (1) thromboembolic event (S0820 study) in this category. While the Investigator listed this event as not related, the Medical Monitor at Cancer Prevention Pharmaceuticals listed this event as possibly related. This is a known risk of sulindac and is listed in the Investigator's Brochure, Reference Safety Information.

The remaining three (3) events were classified as being 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. There was one (1) incidence of gastrointestinal bleeding that was evaluated as probably related to treatment. Gastrointestinal bleeding is an uncommon, but known risk of sulindac.

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 and S0820 Phase III clinical studies.

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 treatment duration for the S0820 (PACES) study is comparable with 3 years of treatment at a dose level of 500 mg/day eflornithine and 150 mg/day sulindac. The minimal toxicities observed to date in CPP FAP-310 for treatment of FAP patients with eflornithine and sulindac for up to 2 years supports the extension of the treatment time in CPP FAP-310 from 2 to up to 3 years at a dose level of 750 mg/day eflornithine and 150 mg/day sulindac.

**Table 1: FAP Study Schedule (Treatment Extension to a Maximum of 36 Months)**

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

## FAP Study Schedule Treatment Extension Footnotes

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

1. Chemistry panel includes – electrolytes (Na, K, CL, CO<sub>2</sub>), 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 patient diaries will be dispensed to the subject every 3 months (month 24, 27, 30, and 33) in person or by special arrangements.
8. Patients 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 patients 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 and 36/EOT visits. For patients 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 patients that have a duodenum.
12. Monthly ( $\pm$  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 patient 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/EOT visit. US and Canada sites only.
15. A random urine sample (15 mL minimum) will be collected at months 24, 30 and 36/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 and 36/EOT visits.
17. EOT visit will occur within 2 weeks off study treatment for any cause including completion of treatment at 36 months.
18. Subject needs to be in the supine position for 10 minutes prior to the EKG, including EKGs collected during PK sampling.
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).

### **8.2.6 Month 24 (+/- 2 weeks)**

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 12 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.

All patients 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. A normal mucosal biopsy sample for polyamine determination will be obtained during the colonoscopy/proctoscopy procedure.

### **8.2.10 Treatment Extension Intervention (Months 25 - 36)**

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 8.2.7, and Table 3 and Table 4 may be eligible to participate in the 12 month 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 visit.
4. Subject was randomized on or before December 31, 2015.
5. 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 and 35 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 visit patients 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 visit, patients 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 urine sample 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 33 month visit patients 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 36 month visit patients 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 sample 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.

#### **8.2.11 Treatment Extension - End of Treatment/Early Termination (+/- 2 weeks)**

Within 2 weeks of final study pill treatment for any cause, all patients 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 Month 36 visit or if the patient has completed at least 3 months of treatment from the previous on-study upper and lower endoscopy procedures (including baseline). A normal mucosal biopsy will be obtained during the colonoscopy/proctoscopy procedure and a urine sample will be collected for polyamine determination.

If the patient 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 normal mucosal biopsy will be obtained during the colonoscopy/proctoscopy procedure and a urine sample will be collected for polyamine determination.

If there is a cumulative delay/suspension of study medication for greater than 90 days from randomization for any reason, the patient will need to be formally taken off-study treatment and complete the End of Treatment (EOT) assessments.

#### **8.2.12 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, patients 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 patient 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.

#### **8.2.13 Termination of Treatment Extension Procedures**

Once all randomized subjects have reached a minimum of 24 months of treatment or have come off study prior to reaching 24 months of treatment, the treatment extension will be closed. Any subject that is active in the treatment extension will be scheduled for an end of treatment visit. This visit should be scheduled within 30 days upon notification of the closure of the treatment extension. Subjects may continue to take study medication until the end of treatment visit.

**Study ID: CPP FAP-310 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)**

**List of Changes for Protocol Amendment**

From Version 4.0, 14March2016 to Version 4.1, 27December2016

Location	Change	Reason for Change
Global Change	<b>Changed:</b> Version 4.0, 14March2016 <b>To:</b> Version 4.1, 27December2016	Update protocol version and date
Section 2.7.3	<b>Added:</b> (Actavis, formerly Watson laboratories, Inc.)	Administrative change
Section 8.2.5	At the month 6, 12 and 18, deleted repeated words "...and urine sample"	Administrative change
Section 8.2.10	at the month 30 and 36, deleted repeated words "...and urine sample"	Administrative change
Section 9.4	Changed 1 <sup>st</sup> paragraph, from ... $\pm$ 2 weeks to $\pm$ 1 week	Administrative change
Section 11.2	Changed 1 <sup>st</sup> paragraph, from ...12 and 24 (end of treatment) to 12, 24 and 36 (end of treatment)	Administrative change
Section 11.9	Fixed formatting	Administrative change
Section 12.1	<b>Deleted 3<sup>rd</sup> paragraph:</b> "The decision to seek regulatory approval based upon the results of the primary objective will be taken sequentially. If the result of comparison 1 is significant at level 0.05, FDA approval will be sought. If comparison 1 is significant, then if the result of comparison 2 is also significant at level 0.05, EMA approval will be sought as well. But if the result of comparison 1 is not significant at level 0.05, neither FDA nor EMA approval will be sought. This procedure is formally equivalent to a closed sequential test procedure for controlling the probability of making a false claim that regulatory criteria are satisfied at level 0.05."	Administrative change
Section 12.1	<b>Revised text from:</b> <del>If the endpoint determination cannot be made at the end of study clinic visit per the pre-specified study requirements, a blinded adjudication committee will review the reasons for such deviations. If upon blinded adjudication it can be determined that a subject's withdrawal is for reasons deemed unrelated to his or her endpoint status, that subject will be treated as a censored observation as of the last patient visit. If upon blinded adjudication it cannot be determined that a subject's withdrawal is unrelated to endpoint status, an imputed primary endpoint will be used in the primary analysis for such withdrawals. The time to this imputed event will be from randomization to the last recorded patient visit. All other subjects who complete their follow-up without a FAP-related event by the end of the study will be treated as a censored observation as of the actual follow-up time for the close-out visit.</del> <b>To:</b> If upon blinded adjudication it can be determined that a subject's withdrawal is for reasons deemed unrelated to his or her endpoint status, that subject will be treated as a censored observation as of the last recorded clinic visit. If upon blinded adjudication the CEC considers the early withdrawal to be consistent with disease progression (not specifically an FAP-related event as defined in the FAP-310 protocol), the patient will be determined to have an imputed FAP-related event. The time to this imputed event will be from randomization to the last recorded clinic visit.	Administrative change
Section 12.4	<b>3<sup>rd</sup> paragraph, revised:</b> To achieve this number of events, 171 subjects have been randomized and some will receive up to 3 years of treatment. <del>we plan to have a 3-year study (with up to 12 months enrollment assuming no sample size reassessment plus 2 years of treatment and follow-up for the last enrolled patients).</del>	Administrative change
Section 12.4.5	<b>Revised:</b> <del>Within the entire patient population there will be subsets who did not receive the full course of per protocol treatment. The patient diary and pill count will define the extent of compliance. This subgroup of patients will be categorized into various cohorts. For consistency, an adjudication committee will be established, to review all study events (i.e., FAP-related events and dropouts) and categorize</del>	Administrative change

Location	Change	Reason for Change
	<p><del>them either as censored observations or imputed endpoints. For exploratory and sensitivity analysis the following dropout subsets will be included in secondary analyses:</del></p> <p><b>To:</b> 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.</p> <p>Since the goal of this trial is to delay the time to FAP-related disease progression, there may be some patients with polyposis progression and/or disease related symptoms who will discontinue treatment. An independent blinded Clinical Events Committee (CEC), also referred to as an adjudication committee will be established (vide infra), to review and confirm all Investigator determined FAP-related events and to assess all other off-study subjects for symptoms or signs of possible disease related progression that may or may not be delineated in the protocol.</p> <p>For exploratory and sensitivity analyses the following dropout subsets will be included in secondary analyses:</p>	
Section 12.7	<p><b>Revised Sentence:</b> For the primary time to event analysis, the only possible patient outcome is an observed FAP-related event, an imputed FAP-related event or a censored observation.</p> <p><b>Deleted:</b></p> <p>A patient will be considered a treatment failure if for any reason, the endpoint determination cannot be made per the pre-specified protocol. The time to this imputed event will be from randomization to the last recorded patient visit. A study event adjudication committee will be formed to further define the methods for defining imputed and censored events. Any secondary or sensitivity analysis that includes this assumption will be clearly noted. Similarly, any sensitivity analysis that incorporates the last observation carried forward (LOCF) method, to compensate for early patient dropouts or missing data, will be clearly noted.</p> <p><b>Added:</b></p> <p>Secondary analysis data include the presence of a specific genetic mutation, and urinary metabolite concentrations (see Section 3.2.2). 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)”.</p>	Administrative change
Section 12.8	<b>2<sup>nd</sup> paragraph, 1<sup>st</sup> sentence deleted:</b> ...“at a later time”....	Administrative change
	<p><b>5<sup>th</sup> paragraph</b></p> <p><b>1<sup>st</sup> sentence added:</b> “A pre-specified interim futility analysis will be conducted in a blinded manner.”</p> <p><b>2<sup>nd</sup> sentence deleted</b> “adjudicated”</p>	Administrative change
Section 15	<b>Added:</b> CEC, Clinical Events Committee (also referred to as an adjudication committee)	Administrative change
END of Changes		

**Study ID: CPP FAP-310 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)**

**List of Changes for Protocol CPP FAP-310 Amendment  
From Version 4.1, 27December2016 to Version 5.0, 21July2017**

Location	Change	Reason for Change
Global Change	Version 4.1, 27December2016 to Version 5.0, 21July2017	Protocol version, date, rev.
Global Change	<b>Fixed:</b> Formatting <b>Corrected:</b> Typographical errors <b>Updated:</b> Table of Contents, listing of tables, reference numbers, table numbers, and section numbers.	Administrative change.
Sec 1.5	<b>Added:</b> Jewell Samadder M.D. as one of the study Co-Principal Investigators <b>Changed:</b> PI for Huntsman Cancer Institute from Jewell Samadder, MD to Priyanka Kanth, MD Updated address for Samir Gupta, M.D.	Administrative change.
Sec 1.6	<b>Deleted:</b> Subjects completing 24 months of treatment without an FAP event can continue treatment for up to 12 additional months until one of the following occurs: 1) subject has an FAP event or comes off study for other reasons, 2) all randomized subjects have reached a minimum of 24 months of treatment or have come off study prior to reaching 24 months of treatment or <b>Revised to:</b> 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: <ol style="list-style-type: none"> <li>1. If randomized between November 2015 and April 2016 eligible for up to 36 months of treatment</li> <li>2. If randomized between May 2015 and October 2015 eligible for up to 42 months of treatment</li> <li>3. If randomized between July 2014 and April 2015 eligible for up to 48 months of treatment</li> </ol> or until one of the following occurs: <ol style="list-style-type: none"> <li>1. Subject has an FAP-related event or comes off study for other reasons</li> <li>2. Trial end-date of April 30, 2019 has been reached</li> <li>3. 90 FAP-related events have occurred</li> <li>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.</li> <li>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</li> </ol>	Changes maximum treatment duration and adds information on initial treatment and treatment extension.
Sec 3.2	<b>Revised</b> Section 3.2 Rationale for Treatment Duration Extension <b>up to 48 Months.</b> Section was rewritten to provide rationale for treatment extension up to 48 months.	Provides the rationale and data for treatment extension duration.
Sec 3.3	<b>Changed</b> “36” to “48”-month maximum treatment	Changes maximum treatment duration.
Sec 4.2	5 <sup>th</sup> bullet point <b>Revised</b> to <ul style="list-style-type: none"> <li>• 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:               <ol style="list-style-type: none"> <li>1. If randomized between November 2015 and April 2016 eligible for up to 36 months of treatment</li> <li>2. If randomized between May 2015 and October 2015 eligible for up to 42 months of treatment</li> <li>3. If randomized between July 2014 and April 2015 eligible for up to 48 months of treatment</li> </ol> </li> </ul> or until one of the following occurs:	Changes maximum treatment duration and adds information on initial treatment, treatment extension and study termination.

**List of Changes for Protocol CPP FAP-310 Amendment**  
**From Version 4.1, 27December2016 to Version 5.0, 21July2017**

Location	Change	Reason for Change
	<ol style="list-style-type: none"> <li>1. Subject has an FAP-related event or comes off study for other reasons</li> <li>2. Trial end-date of April 30, 2019 has been reached</li> <li>3. 90 FAP-related events have occurred</li> <li>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</li> <li>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.</li> </ol>	
Sec 4.4	<b>Revised</b> 1 <sup>st</sup> sentence: “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 <b>the time from the date of randomization to the date of the first occurrence of any FAP-related event</b> in the subject as a whole.”	Clarifies time to an FAP-related event.
Sec 5.1	1 <sup>st</sup> sentence <b>deleted</b> : “Hydrochloride” and “monohydrochloride monohydrate.” 2 <sup>nd</sup> sentence <b>deleted</b> “The clinical dosage form is a yellow, film-coated convex tablet containing 250 mg of eflornithine HCl, monohydrate. <b>Revised with</b> “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).”	Clarifies drug description.
Sec 5.2, 5.2.1, 5.2.2	<b>Added</b> : “(Actavis, formerly...)”	Administrative change.
Sec 7	<b>Revised</b> sentence “Since an individual may have more than one disease site involved, the trial will assess <b>the time from the date of randomization to the date of the first occurrence of any FAP-related event</b> in the subject as a whole.”	Clarifies time to an FAP-related event.
Sec 8.1 Table 4	<b>Updated</b> : Table 4 and footnotes with assessments out to 48 months.	Supports treatment extension duration.
Sec 8.2.4, Table 5	<b>Changed</b> : “36” to “48” months.	Supports treatment extension duration.
Sec 8.2.5	Paragraph 3 and 4 <b>Added</b> : “(± 1 week)” <b>Revised</b> the rest of the section for consistency with Table 3 “Initial 24-month Treatment Intervention Assessments”	Administrative change.
Sec 8.2.6	<b>Revised</b> as follows: 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: <ul style="list-style-type: none"> <li>▪ &gt; 90 days from randomization to month 36</li> <li>▪ &gt; 105 days from randomization to month 42</li> <li>▪ &gt; 120 days from randomization to month 48</li> </ul> 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.	Supports treatment compliance.
Sec 8.2.9	<b>Revised</b> Treatment Extension Intervention (Months 25-48) to be consistent with Table 4, FAP Study Schedule (Treatment Extension to a maximum of 48 months)	Supports treatment extension duration.
Sec 8.2.10	<b>Revised</b> for Treatment extension – End of Treatment/Early Termination 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.	Clarifies treatment extension end of treatment procedures.

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**From Version 4.1, 27December2016 to Version 5.0, 21July2017**

Location	Change	Reason for Change
	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.	
Sec 8.2.12	<p><b>Changed:</b> Once all randomized subjects have reached a minimum of 24 months of treatment or have come off study prior to reaching 24 months of treatment, the treatment extension will be closed. Any subject that is active in the treatment extension will be scheduled for an end of treatment visit. This visit should be scheduled within 30 days upon notification of the closure of the treatment extension. Subjects may continue to take study medication until the end of treatment visit.</p> <p><b>To:</b> Subjects on the treatment extension can continue on treatment for up to 48 months based on their date of randomization as follows:</p> <ol style="list-style-type: none"> <li>1. If randomized between November 2015 and April 2016 eligible for up to 36 months</li> <li>2. If randomized between May 2015 and October 2015 eligible for up to 42 months</li> <li>3. If randomized between July 2014 and April 2015 eligible for up to 48 months</li> </ol> <p>or until one of the following occurs:</p> <ol style="list-style-type: none"> <li>1. Subject has an FAP-related event or comes off study for other reasons</li> <li>2. Trial end-date of April 30, 2019 has been reached</li> <li>3. 90 FAP-related events have occurred</li> <li>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</li> <li>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</li> </ol>	Clarifies treatment extension termination procedures.
Sec 8.2.13	<p><b>Added new section: Treatment Compliance</b></p> <p>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:</p> <ul style="list-style-type: none"> <li>▪ &gt; 90 days from randomization to month 36</li> <li>▪ &gt; 105 days from randomization to month 42 or</li> <li>▪ &gt; 120 days from randomization to month 48</li> </ul>	Supports treatment compliance.
Sec 8.2.14	<p><b>Revised 1<sup>st</sup> sentence to:</b> “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.”</p>	Clarifies time to an FAP-related event.
Sec 8.3.2 #6	<p><b>Added: .....for any reason as follows:</b></p> <ul style="list-style-type: none"> <li>• &gt; 90 days from randomization to month 36</li> <li>• &gt; 105 days from randomization to month 42</li> <li>• &gt; 120 days from randomization to month 48</li> </ul>	Supports subject treatment compliance.
Sec 10.2	<b>Changed:</b> months 12, 24, and 36 <b>To</b> months 12, 24, 36 and 48	Supports treatment extension duration.
Sec 11.1, 11.3	<b>Changed:</b> months 3,6,12,18,27,30 and 36 <b>To</b> months 3, 6, 12, 18, 24, 30, 36, 42 and 48/	Supports treatment extension duration.
Sec11.2	<p><b>Changed:</b> months 12, 24 and 36 <b>To</b> months 12, 24, 36 and 48</p> <p><b>Changed:</b> months 3,6,12,18,24,30 and 36 <b>To</b> months 3, 6, 12, 18, 24, 30, 36, 42 and 48</p>	Supports treatment extension duration.
Sec 11.5	<b>Revised</b> “For the EU, Reference Safety Information is located in the IB Ver CPP-201-IB05 and subsequent versions” <b>To</b> “The Reference Safety Information (RSI) is located in the IB Ver. CPP-201-IB08 and subsequent versions, which...”	Administrative change.

**List of Changes for Protocol CPP FAP-310 Amendment**  
**From Version 4.1, 27December2016 to Version 5.0, 21July2017**

Location	Change	Reason for Change
Sec 11.7	<b>Added:</b> 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).	Clarifies safety reporting procedures.
Sec 11.8	<b>Revised Section:</b> <ul style="list-style-type: none"> <li>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.</li> <li>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 <i>[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]</i>. 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.</li> </ul>	Clarifies pregnancy reporting and procedures.
Sec 11.9	<b>Added:</b> off study treatment date, "and concomitant medications for AES recorded within the 30-day post-EOT."	Clarifies safety reporting procedures.
Sec 12	<b>Revised sentence first paragraph:</b> "... than each agent alone in delaying <b>the time from the date of randomization to the date of the first occurrence of any FAP-related event</b> in Familial Adenomatous Polyposis (FAP) patients." <b>Changed:</b> 12 to 24 months <b>Revised</b> 4 <sup>th</sup> paragraph, ITT definition as follows: For the primary efficacy analyses, we will use the intent-to-treat (ITT) population, defined as all subjects <b>that have been randomized to one of the three study arms</b> .	Clarifies time to an FAP-related event.  Clarifies (ITT) population.
Sec 12.1	<b>Revised as follows</b> "...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: <ol style="list-style-type: none"> <li>CPP-1X placebo + sulindac active vs. CPP-1X active + sulindac active,</li> <li>and</li> <li>CPP-1X active + sulindac placebo vs. CPP-1X active + sulindac active</li> </ol> The combination of CPP-1X active + sulindac active is specified as the reference treatment because it is common to both comparisons. The analytic method for the primary analysis will be a time-to-event analysis using the stratified log-rank test, as previously described. The discrete time version of the log-rank statistic using visit month number 0, 6, 12, 18, 24, 30, 36, 42, 48 will be used. Stratified discrete-time Cox proportional hazards regression models will be used for secondary assessments. <sup>85</sup> Graphical analyses (log-minus-log plots) will be used to check the assumption of constant hazard ratios. <del>The analytic method for the primary analysis will be a time to event analysis using the stratified log-rank test. Cox proportional hazards regression models will be used for secondary assessments.<sup>85</sup> Graphical analyses (log minus log plots) will be used to check the assumption of constant hazard ratios.</del>	Supports primary efficacy objective and analysis.

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**From Version 4.1, 27December2016 to Version 5.0, 21July2017**

Location	Change	Reason for Change
	<p>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's withdrawal is for reasons deem unrelated to his or her endpoint status, that subject will be treated as a censored observation as of the last recorded clinic visit (endoscopic disease assessment). <del>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 upon blinded adjudication it can be determined that a subject's withdrawal is for reasons deemed unrelated to his or her endpoint status, that subject will be treated as a censored observation as of the last recorded clinic visit. If upon blinded adjudication the CEC considers the early withdrawal to be consistent with disease progression (not specifically an FAP-related event as defined in the CPP FAP-310 protocol), the patient will be determined to have an imputed FAP-related event. The time to this imputed event will be from randomization to the last recorded clinic visit.</del></p>	
Sec 12.4	<p><b>Revised the following:</b></p> <p>1) The level of statistical significance is set at 0.05, using a 2-sided log-rank test for time-to-first FAP-related event in discrete time (visit month number), 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)</p> <p>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;</p> <p><b>Added:</b> The following calculations are based on our review of limited single-agent data for eflornithine and sulindac, in which the 2-year event free rates imply a single overall event free rate of 60% for combination treatment group and 30% in each single agent treatment group.</p> <p><b>Deleted</b> last paragraph: <del>This is based on our review of limited single agent data for eflornithine and sulindac, in which the 2-year event free rates imply a single overall event free rate of 60% for combination treatment group and 30% in each single agent treatment group.</del></p>	Supports sample size determination.
Sec 12.5.1	<b>Revised ITT definition:</b> "The intent-to-treat population includes all patients that have been randomized to one of the three study arms (CPP-1X plus sulindac,.....)"	Clarifies (ITT) population.
Sec 12.5.4	<p><b>Added:</b> These results will be for quality assurance purposes and will not be used for the primary endpoint analysis to assess clinical benefit.</p> <ul style="list-style-type: none"> <li>• CEC reviewed and adjudicated subject outcomes</li> </ul> <p><b>Deleted:</b> the following <del>dropout</del> subsets</p>	Clarifies (ITT) population.
Sec 12.6.2	<b>Deleted:</b> ...non-compliance for more than 90 days, withdrawals ...	Administrative change.
Sec 12.6.5	<p><b>Added:</b> 42 and 48 assessment points</p> <p><b>5<sup>th</sup> para deleted:</b> "This trial has three strata and three treatment options with 150 patients to be entered."</p>	Supports treatment extension duration. Administrative change.
Sec 12.6.6	<b>Added:</b> 36, 42 and 48 assessment points.	Supports treatment extension duration.
Sec 12.7	<b>3<sup>rd</sup> paragraph deleted:</b> "(See Section 3.2.2)"	Administrative change.
Sec 12.8	<p><b>5<sup>th</sup> paragraph changed from:</b></p> <p>For the futility interim analysis, the futility stopping criterion of <math>Z=0.50</math> is one-sided, and corresponds to a conditional power criterion of approximately 0.12 (to two decimals). That is, assuming between 52 and 55 expected total number of events have occurred by trial end in either of the two-arm comparisons, 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, then under the design alternative hazard ratio of 0.4243, there would be only a 12% probability (or less) 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</p>	Clarifies futility analysis procedures.

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**From Version 4.1, 27December2016 to Version 5.0, 21July2017**

Location	Change	Reason for Change
	<p>be reasonable for the DMC to consider stopping the trial for futility. The futility analysis results will be presented in a simple manner whereby the DMC will be informed that the conditions indicating futility have been met (i.e. the futility boundary has been crossed, yes or no). Unless the DMC requires it on ethical grounds, no early stopping for positive efficacy is proposed.</p> <p><b>To:</b> The futility analysis will be performed for each of the two treatment comparisons contained in the primary objective:</p> <ol style="list-style-type: none"> <li>1. CPP-1X placebo + sulindac active vs. CPP-1X active + sulindac active,</li> <li>and</li> <li>2. CPP-1X active + sulindac placebo vs. CPP-1X active + sulindac active</li> </ol> <p>The futility analysis efficacy component 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.</p> <p>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 <math>Z = -0.50</math>. That is, if the Z-score is less than or equal to <math>-0.50</math>, 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 <math>Z = -0.50</math> 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 <math>-0.5</math> (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.</p> <p>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.</p>	
END of Changes		

**Study ID: CPP FAP-310 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)**

**List of Changes for Protocol CPP FAP-310 Amendment  
From Version 5.0, 21July2017 To Version 5.1, 09April2018**

Location	Change	Reason for Change
Global	Version 5.0, 21July2017 to Version 5.1 09April2018	Admin. change.
Sec. 4.3	Changed “A total of 150 eligible patients...” To “At least 150 eligible patients...”	Admin. Change for consistency with Sec. 12.0
Sec. 12.0	3 <sup>rd</sup> para <b>Revised</b> “A total of 150 eligible patients will be enrolled in this study, 50 per treatment group.” To “At least 150 eligible patients will be enrolled in this study, with at least 50 per treatment group.”	To be consistent with language in SAP Ver. 5.0, April 02, 2018.
Sec. 12.1	5 <sup>th</sup> para <b>Deleted</b> “The discrete time version of the log rank statistic using visit month number 0, 6, 12, 18, 24, 30, 36, 42, 48 will be used.” Changed “Stratified discrete time...” To The stratified Cox proportional hazards.....”  7 <sup>th</sup> para, 2 <sup>nd</sup> sentence <b>Revised</b> to read “If a subject withdraws, that subject will be treated as a censored observation.....”  9 <sup>th</sup> para <b>Revised</b> “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 the primary analysis using a stratified Cox model including that term in addition to the treatment arm. The covariate-adjusted score test (adjusted stratified log-rank test) will serve as the primary result for the trial.”  <b>To</b> “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.	To be consistent with language in SAP Ver. 5.0, April 02, 2018.
Sec. 12.4	<b>Deleted and Revised text that follows.</b> <b>Deleted</b> “For the purposes of power calculations, we assume the following:  1) The level of statistical significance is set at 0.05, using a 2-sided log-rank test for time-to-first FAP-related event in discrete time (visit month number), 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)  2) A doubling of the time to occurrence of the primary event 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 the same event rate.  The following calculations are based on our review of limited single-agent data for eflornithine and sulindac, in which the 2-year event free rates imply a single overall event	To be consistent with language in SAP Ver. 5.0, April 02, 2018.

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**From Version 5.0, 21July2017 To Version 5.1, 09April2018**

Location	Change	Reason for Change
	<p>free rate of 60% for combination treatment group and 30% in each single agent treatment group.</p> <p>For this situation, 49 events would be needed for the two-group situation at the 2-sided 0.05 level with 85% power and the doubling of the time to primary event.<sup>88,89</sup> Assuming two-year event proportions of 70% in either of the two single-agent groups and 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 20 in the combination arm. Thus we expect to have 55 patients with a FAP-related event in each comparison, achieving almost 89% power. The standard deviation around this expectation is 4.74, so we would be highly likely to observe at least the required 49 events. Even if the total number of events in either comparison were only 43, there will still be 80% power to detect the design effect size, namely, a hazard rate ratio of <math>(\log 0.30)/(\log 0.60)</math> corresponding to the doubling of event-free follow-up over two years (approximately equal to 2.3569). For completeness, the design effect size is equivalent to a hazard rate ratio of <math>(\log 0.60)/(\log 0.30)</math> for the combination treatment relative to a single-agent treatment (approximately equal to 0.42428).</p> <p>In total we expect to observe <math>35+35+20=90</math> primary endpoints among the three groups (plus or minus 5.7).”</p> <p><b>Revised to</b> “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).</p> <p>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.</p> <p>For the purposes of power calculations, we assume the following:</p> <ol style="list-style-type: none"> <li>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;</li> <li>2) A doubling of the two-year event-free proportion from either of the single agent treatment arms to the combination treatment group;</li> <li>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;</li> <li>4) The two single-agent treatment groups have approximately the same event rate.</li> </ol> <p>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.</p> <p>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</p>	

**List of Changes for Protocol CPP FAP-310 Amendment**  
**From Version 5.0, 21July2017 To Version 5.1, 09April2018**

Location	Change	Reason for Change
	<p>event-free proportions into hazard ratios under a simplifying assumption of exponentially distributed time-to-event.</p> <p>Furthermore, the stratified log-rank test is an optimal test (locally most powerful) under the assumption that the <i>ratio</i> 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 <i>design alternative parameter</i> for the trial.</p> <p>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 <math>\{\log(0.60) / \log(0.30)\} = 0.4243</math>. <i>This is the design alternative hazard ratio for this trial</i> 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 <i>at least</i> 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 = <math>\{\log(0.70) / \log(0.30)\}</math>.</p> <p>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 <math>\{\log(0.30) / \log(0.60)\} = 1/0.4243 = 2.357</math>.</p> <p>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.<sup>88,89</sup> 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.</p> <p>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."</p>	
Sec. 12.5.4	<p><b>Deleted</b> "Since the goal of this trial is to delay the time to FAP-related disease progression, there may be some patients with polyposis progression and/or disease related symptoms who will discontinue treatment. An independent blinded Clinical Events Committee (CEC), also referred to as an adjudication committee will be established (vide infra), to review and confirm all Investigator determined FAP-related events and to assess all other off-study subjects for symptoms or signs of possible disease related progression that may or may not be delineated in the protocol. These results will be for quality assurance purposes and will not be used for the primary endpoint analysis to assess clinical benefit."</p> <ul style="list-style-type: none"> <li>• "CEC reviewed and adjudicated subject outcomes"</li> </ul>	To be consistent with language in SAP Ver. 5.0, April 02, 2018.

**List of Changes for Protocol CPP FAP-310 Amendment**  
**From Version 5.0, 21July2017 To Version 5.1, 09April2018**

Location	Change	Reason for Change
Sec. 12.6.6	<b>Added</b> “(only if end of treatment)” after 42 months	
Sec. 12.7	<b>Deleted</b> “Secondary analysis data include the presence of a specific genetic mutation, and urinary metabolite concentrations (see Section <b>Error! Reference source not found.</b> ). The primary analysis of the secondary objectives will include collected data only, without imputing or weighting data to compensate for missing data. Sensitivity analyses of these data will be performed to explore study results more fully, in a manner consistent with ICH Guidance “ <i>E9 Statistical Principles for Clinical Trials (February, 1998)</i> ”.	Administrative, repeat of the 3 <sup>rd</sup> paragraph.
END of Changes		

**Study ID: CPP FAP-310 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)**

**List of Changes for Protocol CPP FAP-310 Amendment**

**From Version 5.1, 09April2018 to Version 5.2, 17January2019**

Location	Change
Global	<p>Version 5.1 09April2018 to Version 5.2, 17January2019</p> <p>All administrative revisions in this amendment were made to be consistent with the language in the SAP Ver. 5.1 and Ver. 5.2.</p>
Global	<p><b>Updated:</b> Table of Contents, listing of tables, reference numbers, and section numbers.</p> <p><b>Updated:</b> Minor typographical errors</p>
Sec. 4.5	<p><b>Deleted:</b></p> <p>Secondary efficacy outcomes in this study will include the following:</p> <p style="padding-left: 40px;">To evaluate the potentially effect modifying properties of:</p> <ol style="list-style-type: none"> <li>a. Presence or absence of an ODC polymorphism</li> <li>b. The excretion of 4 urinary polyamines (diacetylspermine, n1-acetylspermidine, n8-acetylspermidine and decarboxylated SAM).</li> </ol> <p><b>Revised to:</b></p> <p><b>Secondary Efficacy Analyses:</b></p> <p>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).</p> <p><b>Deleted:</b></p> <ol style="list-style-type: none"> <li>1. 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).</li> <li>2. Safety outcomes will be assessed by summary analysis of adverse events and clinical laboratory abnormalities.</li> <li>3. Pharmacokinetic outcomes will be assessed by evaluating the population pharmacokinetics for CPP-1X (eflornithine) and sulindac.</li> <li>4. Evaluate tissue and dietary polyamine levels.</li> <li>5. Subject reported quality of life will be evaluated using HRQoL and subject utilities.</li> <li>6. A pilot evaluation of an FAP-specific assessment, the time to the first FAP-related beneficent event, will be studied. This will involve analyzing the endoscopic polyposis data for regression of pre-colectomy colorectal polyposis, rectal/pouch polyposis, and regression of duodenal polyposis.</li> <li>7. An analysis of the components and subgroups included in the primary analysis, and their contribution to the primary outcome.</li> </ol> <p><b>Revised with:</b></p> <p><b>Other Secondary Outcomes in this Study Include the Following:</b></p>

**List of Changes for Protocol CPP FAP-310 Amendment**  
**From Version 5.1, 09April2018 to Version 5.2, 17January2019**

Location	Change
	<p>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).</p> <p>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.</p> <p>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.</p> <p>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).</p> <p>The subcategories of FAP events will be explored by disease stratum groups, and by disease site subgroups.</p> <p>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.</p> <p>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.</p> <p>Patient reported health related quality of life measures will be evaluated using HRQoL.</p> <p>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.</p> <p>Safety outcome data and analyses are described in detail in the Statistical Analysis Plan.</p>
<b>Sec. 12.1</b>	<p><b>Added after 2<sup>nd</sup> paragraph:</b></p> <p>These two treatment comparisons will be performed sequentially as described below.</p> <p>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.</p> <p>Each comparison will be performed at the 2-sided 0.05 level of statistical significance.</p> <p>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.</p> <p>CPP will sequentially perform the two primary comparisons as part of the primary analysis, each at the 2-sided <math>p = 0.05</math> 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.</p> <p>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</p>

**List of Changes for Protocol CPP FAP-310 Amendment**  
**From Version 5.1, 09April2018 to Version 5.2, 17January2019**

Location	Change
	<p>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.</p> <p><b>Deleted:</b></p> <p>The combination of CPP-1X active + sulindac active is specified as the reference treatment because it is common to both comparisons.</p> <p>Each comparison will be performed at the 2-sided <math>p = 0.05</math> level.</p> <p><b>deleted from 9<sup>th</sup> paragraph:</b> “as previously described.”</p> <p><b>Added new 11<sup>th</sup> paragraph:</b></p> <p>“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.”</p>
<p><b>Sec. 12.2</b></p>	<p><b>Deleted:</b></p> <p>Secondary efficacy outcomes in this study will include the following:</p> <p style="padding-left: 40px;">To evaluate the potentially effect modifying properties of:</p> <ol style="list-style-type: none"> <li>a. Presence or absence of an ODC polymorphism</li> <li>b. The excretion of 4 urinary polyamines (diacetylspermine, n1-acetylspermidine, n8-acetylspermidine and decarboxylated SAM)</li> </ol> <p>These secondary variables will be assessed regardless of study outcome, but their use as potential label claims will only apply if a statistically significant treatment effect is found in the primary analysis. For the secondary efficacy analysis, for each secondary variable, a corresponding term will be added to the primary analysis as well as an interaction term (product of the treatment indicator and secondary variable). The coefficient of the interaction term (only) will be tested to determine if the secondary variable alters the magnitude of the treatment effect. Corresponding to each of the two primary analyses, the Hochberg step-up method will be employed to control the overall family-wise error rate with overall alpha set at the two-sided 0.05 level.</p> <p><b>Added:</b></p> <p>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).</p> <p>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.</p> <p>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</p>

**List of Changes for Protocol CPP FAP-310 Amendment**  
**From Version 5.1, 09April2018 to Version 5.2, 17January2019**

Location	Change
	<p><i>any positive improvement</i> at either month 6 (compared to baseline) or at month 12 (compared to baseline or month 6), under the condition that there be <i>no worsening at either timepoint</i> (compared to the preceding timepoint). Refer to the Statistical Analysis Plan for further details on the planned analysis.</p>
12.3	<p><b>Deleted:</b></p> <ol style="list-style-type: none"> <li>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).</li> <li>Safety outcomes will be assessed by summary analysis of adverse events and clinical laboratory abnormalities.</li> <li>Pharmacokinetic outcomes will be assessed by evaluating the population pharmacokinetics for CPP-1X (eflornithine) and sulindac.</li> <li>Evaluate tissue and dietary polyamine levels.</li> <li>Patient reported quality of life will be evaluated using HRQoL and patient utilities.</li> <li>A pilot evaluation of an FAP-specific assessment, the time to the first FAP-related beneficent event, will be studied. This will involve analyzing the endoscopic polyposis data for regression of pre-colectomy colorectal polyposis, rectal/pouch polyposis, and regression of duodenal polyposis.</li> <li>An analysis of the components and subgroups included in the primary analysis, and their contribution to the primary outcome.</li> </ol> <p><b>Added:</b></p> <p>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.</p> <p>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.</p> <p>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).</p> <p>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).</p> <p>The subcategories of FAP events will be explored by disease stratum groups, and by Disease Site subgroups (refer to the Statistical Analysis Plan).</p> <p>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.</p> <p>The excretion of 5 urinary polyamines (diacetylspermine, n1-acetylspermidine, n8-acetylspermidine, decarboxylated SAM, and putrescine) will be assessed in relation to treatment</p>

**List of Changes for Protocol CPP FAP-310 Amendment**  
**From Version 5.1, 09April2018 to Version 5.2, 17January2019**

Location	Change
	<p>group and outcome, using the single point concentration data gathered from the urine samples harvested at each study visit.</p> <p>Patient reported health related quality of life measures will be evaluated using HRQoL (refer to Statistical Analysis Plan for more details).</p> <p>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.</p>
<b>Sec. 12.4</b>	<p><b>Deleted statement after 2<sup>nd</sup> paragraph:</b> “For the purpose of power calculations, we assume the following:” and <b>Inserted section title:</b> 12.4.1 Power Calculation Assumptions:</p> <p><b>After 2<sup>nd</sup> paragraph from section 12.4.1, inserted section title:</b> 12.4.2 Hazard Rates</p>
<b>Sec. 12.8</b>	<p><b>Added above paragraph 5 header:</b> “Prespecified Interim Efficacy and Futility Analysis”</p> <p><b>Revised first sentence under this header to:</b> “A pre-specified interim <i>efficacy and</i> futility analysis...” <b>Deleted from 2<sup>nd</sup> sentence:</b> “futility”; <b>added last sentence:</b> Refer to the Statistical Analysis Plan for more details.</p> <p><b>Changed, 2<sup>nd</sup> paragraph:</b> “The futility analysis <b>To</b> “The analysis.....”</p> <p><b>Changed: 3<sup>rd</sup> paragraph:</b> The futility analysis efficacy component... <b>To:</b> the efficacy analysis...</p>
<b>Sec. 15</b>	<p>Deleted from the listing of Abbreviations</p> <p>CEC, Clinical Events Committee (also referred to as an adjudication committee)</p> <p><b>Added:</b> LGIOI: LGI Observed Improvement; UGIOI: UGI Observed Improvement</p>
<b>END of Changes</b>	

## **STATISTICAL ANALYSIS PLAN**

### **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)**

Protocol Number: CPP FAP-310

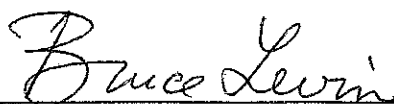
Statistical Analysis Plan

Version: Ver. 2.0, April 11, 2013

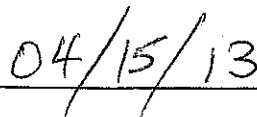
Sponsor: Cancer Prevention Pharmaceuticals, Inc.  
1760 E. River Road, Suite 250  
Tucson, AZ 85718  
Phone: 520-908-7774  
Fax: 520-232-2191

## STATISTICAL ANALYSIS PLAN (SAP) SIGNATURE SHEET

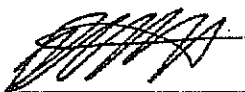
The undersigned have reviewed the format and content of this Statistical Analysis Plan (SAP) for Cancer Prevention Pharmaceuticals, Inc. study CPP FAP-310 titled "A DOUBLE-BLIND, RANDOMIZED, PHASE III TRIAL OF THE SAFETY AND EFFICACY OF CPP-1X/SULINDAC COMPARED WITH CPP-1X, SULINDAC AS SINGLE AGENTS IN PATIENTS WITH FAMILIAL ADENOMATOUS POLYPOSIS (FAP)" and have approved this SAP as finalized.



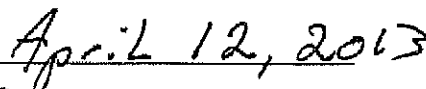
Bruce Levin, Ph.D.  
Statistician



Date



Robert B. MacArthur, Pharm.D., M.S.  
Clinical Affairs and Development



Date

Alfred M. Cohen, M.D.  
Chief Medical Officer

Date

**STATISTICAL ANALYSIS PLAN (SAP) SIGNATURE SHEET**

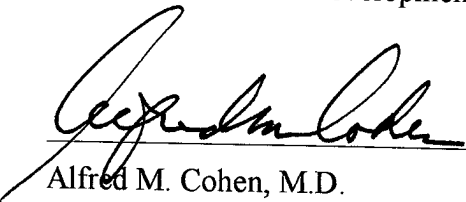
The undersigned have reviewed the format and content of this Statistical Analysis Plan (SAP) for Cancer Prevention Pharmaceuticals, Inc. study CPP FAP-310 titled "A DOUBLE-BLIND, RANDOMIZED, PHASE III TRIAL OF THE SAFETY AND EFFICACY OF CPP-1X/SULINDAC COMPARED WITH CPP-1X, SULINDAC AS SINGLE AGENTS IN PATIENTS WITH FAMILIAL ADENOMATOUS POLYPOSIS (FAP)" and have approved this SAP as finalized.

\_\_\_\_\_  
Bruce Levin, Ph.D.  
Statistician

\_\_\_\_\_  
Date

\_\_\_\_\_  
Robert B. MacArthur, Pharm.D., M.S.  
Clinical Affairs and Development

\_\_\_\_\_  
Date

  
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Alfred M. Cohen, M.D.  
Chief Medical Officer

4/12/13  
\_\_\_\_\_  
Date

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**1. LIST OF ABBREVIATIONS**

<b>Abbreviation</b>	<b>Term</b>
AE	Adverse Event
ANCOVA	Analysis of covariance
CPP	Cancer Prevention Pharmaceuticals, Inc.
CPP-1X	Eflornithine, DFMO, Difluoromethylornithine
CTCAE	Common Terminology Criteria for Adverse Events
DMC/DSMB	Data Monitoring Committee/Data Safety Monitoring Board
EFS	Event-Free Survival
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
FAP	Familial Adenomatous Polyposis
FDA	Food and Drug Administration
FFQ	Food Frequency Questionnaire
HRQoL	Health Related Quality of Life
ICH	International Conference on Harmonization
ITT	Intent-To-Treat
LOCF	Last Observation Carried Forward
NASR	Nutrition Assessment Shared Resource (Fred Hutchinson Cancer Research Center)
NCI	National Cancer Institute
ODC	Ornithine Decarboxylase
QLQ	Quality of Life Questionnaire
SAM	S-Adenosyl Methionine
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System

## 2. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the proposed statistical analysis of the Cancer Prevention Pharmaceuticals, Inc. (CPP) study CPP FAP-310 entitled: “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)”.

The purpose of this document is to apply sound analytic principles through description and pre-specification of the statistical approaches and data handling conventions for key analyses and the randomization processes.

This plan will focus on analysis of the primary and secondary endpoints, intended to assess the extent to which the combination treatment (CPP-1X 750 mg daily + sulindac 150 mg daily) is more effective than each of the two single agent treatments alone (CPP-1X 750 mg daily + placebo, and sulindac 150 mg daily + placebo) in delaying the time to the first FAP-related event in FAP patients. Sample size and total FAP related events will be discussed, along with study population definitions. In addition, we will summarize our approach regarding the analysis of safety data, pharmacokinetic data, and patient reported quality of life data. The composition, charter, and initial tasks of the Data Monitoring Committee (DMC) will be described, along with planned interim analyses.

## 3. STUDY OBJECTIVES AND ENDPOINTS

### 3.1 Overview of Study

This is a randomized, double-blind, phase III trial in patients with FAP to evaluate the safety and efficacy of the combination product 750 mg CPP-1X + 150 mg sulindac versus each of the two single-agent products: 1) 750 mg CPP-1X; and 2) 150 mg sulindac. The primary study comparisons will be made between the combination product and each single agent product, separately.

Eligible patients who have given informed consent will enter the study with the intent to participate for the full treatment period of 24 months. Accrual is expected to take 6 – 12 months.

A stratified randomization procedure will be used 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 patient as a whole. In order to minimize potential treatment arm imbalance a centralized randomization process will be used to balance treatment groups within disease prognostic strata.

The stratification is predicated on the following projected event rates for the disease site specific eligibility criteria (rectal/pouch polyposis, duodenal polyposis, pre-colectomy) which are provided in the clinical study protocol (Appendix D) and summarized in Table 3.1.

**Table 3.1 Projected Event Free Rate by Disease Site**

Disease Site	Projected 2-year Event Free Rate Without Treatment
Rectum/Pouch Polypsis	Excisional intervention and/or high risk adenoma – 40 - 60%
Duodenal Polypsis	Excisional intervention, Spigelman stage progression, cancer – 50%
Pre-colectomy	Colectomy, proctocolectomy – 10%

The stratified randomization will be reflected in stratified analyses for the primary and secondary endpoints. For design purposes only, however, the following simplified assumptions were made: an overall event free proportion of 30% in the single agent treatment group and 60% in the combination treatment group after 24 months of study treatment. This is described further in Table 3.2 below. See Section 5.1 for sample size and power calculations.

**Table 3.2 Overall Event Free Proportions After Two Years of Follow-up\***

Treatment	S(t)	t (months)	Median Time to Event (months)
Combination	0.6	24	32.566
Single Agent	0.3	24	13.817

\*These proportions are assumed for design purposes only. The median times to event are based on the assumption of an exponential time-to-event function S(t) in each group.

A total of 150 eligible patients will be enrolled in this study, 50 per treatment group. Patients will be randomized to one of three treatment groups within the prognostic strata defined above 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 patients nor Investigator nor Sponsor will be aware of treatment assignment.

The grading of adverse events will be based on the current version of the NCI Common Terminology Criteria for Adverse Events (CTCAE Version 4).

Refer to the CPP FAP-310 protocol for the details of the treatment and study schedule, and description of study procedures and tests.

### 3.2 Study Objectives and Primary Hypothesis Testing

The primary study analysis will be performed using the intent-to-treat (ITT) population (see Section 4.1)

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 time to the first occurrence of any FAP-related event.

Thus the primary objective contains two treatment comparisons:

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

Each comparison will be performed at the 2-sided  $p = 0.05$  level.

As explained in Section 3.2.1 below, the decision to seek regulatory approval based upon the results of the primary objective will be taken sequentially.

If the result of comparison 1 is significant at level 0.05, FDA approval will be sought. If comparison 1 is significant, then if the result of comparison 2 is also significant at level 0.05, EMA approval will be sought as well. But if the result of comparison 1 is not significant at level 0.05, neither FDA nor EMA approval will be sought. This procedure is formally equivalent to a closed sequential test procedure for controlling the probability of making a false claim that regulatory criteria are satisfied at level 0.05.

### **3.2.1 Regulatory Review of Primary Outcome Compliance**

CPP has received advice from both the FDA and the EMA concerning the test method and criteria (Sections 3.2 and 5) to be used when analyzing the primary study outcome, including the value of alpha.

The US Food and Drug Administration (FDA) noted that the comparison of CPP-1X + sulindac vs. CPP-1X + placebo will not provide information about the treatment effect of CPP-1X (i.e. eflornithine), and therefore this result will not be included in the product label. Therefore the primary analysis of import to FDA is the comparison of CPP-1X + sulindac vs. sulindac + placebo.

The European Medicines Agency (EMA) noted that for the three arm trial design the superiority of the combination treatment must be tested against both mono-components. The combination treatment must be shown to be superior to both mono-components, or else the results will be considered inconclusive. As a consequence, consistent with EMA/SWAP commentary, alpha does not need to be adjusted for multiplicity and two separate 5% two-sided test will suffice.

To harmonize the advice provided by these two Agencies, CPP will perform two 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.

### **3.2.2 Secondary Efficacy Analyses**

1. To evaluate the potentially effect-modifying properties of:
  - a. Presence or absence of an ODC polymorphism.
  - b. To evaluate the excretion of 4 urinary polyamines (diacetylspermine, n1-acetylspermidine, n8-acetylspermidine, and decarboxylated SAM).

These five secondary variables will be assessed regardless of study outcome, but their use as potential label claims will only apply if a statistically significant treatment effect is found in the primary analysis. For the secondary efficacy analysis, for each secondary variable, a corresponding term will be added to the primary analysis as well as an interaction term (product of the treatment indicator and secondary variable). The coefficient of the interaction term (only) will be tested to determine if the secondary variable alters the magnitude of the treatment effect. Corresponding to each of the two primary analyses, the Hochberg step-up method[1] will be employed to control the overall family-wise error rate with overall alpha set at the two-sided 0.05 level.

### 3.2.3 Other Secondary Outcomes

1. Safety outcomes will be assessed by summary analysis of adverse events and clinical laboratory abnormalities.
2. Pharmacokinetic outcomes will be assessed by evaluating the population pharmacokinetics for CPP-1X (eflornithine) and sulindac.
3. Evaluate tissue and dietary polyamine levels.
4. Patient reported quality of life will be evaluated using HRQoL and patient utilities.
5. A pilot evaluation of an FAP-specific assessment, the time to the first FAP-related beneficent event, will be studied. This will involve analyzing the endoscopic polyposis data for regression of pre-colectomy colorectal polyposis, rectal/pouch polyposis, and regression of duodenal polyposis.
6. An analysis of the components and subgroups included in the primary analysis, and their contribution to the primary outcome.

## 4. POPULATIONS FOR ANALYSIS

### 4.1 Intent-to-Treat (ITT) Population

The intent-to-treat population includes all patients who have signed a voluntary and fully informed consent form, have been deemed eligible to participate by the Investigator based on the screening assessments, and have been randomized to one of the three study arms. Patients 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.

### 4.2 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 according to which actual treatment was initially received.

### 4.3 Per Protocol Population

The per-protocol population is defined as the subset of the ITT population who completed all 24 months of treatment and have primary endpoint determinations performed per protocol specifications.

### 4.4 Other Populations

Within the entire study patient population there will be subsets who did not receive 24 months of daily medication. The patient diary and pill count will define the extent of compliance. This subgroup of patients will be categorized into various cohorts only for purposes of exploratory and sensitivity analysis, including:

- Patients 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.

## 5. DETERMINATION OF SAMPLE SIZE AND STATISTICAL METHODS

### 5.1 Determination of Sample Size

For the purposes of power calculations, we assume the following:

- 1) The level of statistical significance is set at 0.05, using a 2-sided log-rank test for time-to-first FAP-related event, for each of the two between-group comparisons (i.e. CPP-1X plus sulindac vs. CPP-1X and CPP-1X plus sulindac vs. sulindac);
- 2) A doubling of the time to occurrence of the primary event 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 the combination arm vs. either of the two single treatment arms;
- 4) The two single-agent treatment groups have the same event rate.

For this situation, 49 events would be needed for each two-group comparison at the 2-sided 0.05 level with 85% power and the doubling of the time to primary event[2]. Assuming two-year event proportions of 70% in either of the two single-agent groups and 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 20 in the combination arm. Thus we expect to have 55 patients with a FAP related event in each comparison, achieving almost 89% power. The standard deviation around this expectation is 4.74, so we would be highly likely to observe at least the required 49 events. Even if the total number of events in either comparison were only 43, there will still be 80% power to detect the design effect size, namely, a hazard rate ratio of  $0.4243 = (\ln 0.60)/(\ln 0.30)$  corresponding to the doubling of event-free follow-up over two years.

In total we expect to observe  $35+35+20=90$  primary endpoints among the three groups (plus or minus 5.7). To achieve this number of events, we plan to have a 3 year study (with up to 12 months enrollment assuming no sample size reassessment plus 2 years of treatment and follow-up for the last-enrolled patients).

This is based on our review of limited single-agent data for eflornithine and sulindac, in which the 2-year event free rates imply a single overall event free rate of 60% for combination treatment group and 30% in each single agent treatment group. This is described further in Table 5.1 below.

**Table 5.1 Estimated Overall Event Free Proportions after Two Years of Follow-up**

Treatment	S(t)	t (months)	Median Time to Event (months)*
Combination	0.6	24	32.5660
Single Agent	0.3	24	13.8172

\*Based on an assumed exponential time-to-event distribution.

## 5.2 Data Monitoring Committee (DMC)

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 at a later time 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 (A versus B) 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, 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 (based on a blinded A/B comparison).

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 perform an assessment of 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 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. With this approach study enrollment can continue uninterrupted at the study sites, if it is decided to increase study sample size.

The futility assessment will occur when approximately 50% of maximum trial information has been amassed. Assuming a constant enrollment rate over 1 year and full enrollment achieved at one year, that would occur at approximately 1.5 years from enrollment start. At that time patients would have an average of approximately 1.0 year on study treatment. The details of the futility analysis are provided in Table 5.2 below. Unless the DMC requires it on ethical grounds, no early stopping for positive efficacy is proposed.

**Table 5.2 Interim Futility Analysis Details**

Estimated Look Time Point	Description
1.5 years	<p>Efficacy criterion <math>Z=1.96</math> at terminal analysis.</p> <p>Futility criterion of <math>Z=0.50</math> at interim analysis.</p> <p>Total Type I error for end of study comparison = 0.0471.</p> <p>NB: Assuming D = 52 events, power = 0.8566. Assuming D = 55 events, power = 0.8750.</p>

## **5.3 Statistical Methods**

### **5.3.1 Demographic and Baseline Characteristics**

Patients in the three populations (see Section 4) 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 and the institution at which each patient registered, among other features. Baseline characteristics will include laboratory values and disease-related characteristics, as well as any other relevant values (Tables 9.1-9.3 Section 9, Appendices). 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)[3].

### **5.3.2 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.

Patient disposition and treatment will be summarized for the ITT and safety populations defined previously. Patient disposition will be consistent with the CONSORT criteria[4], and will include per treatment group enumeration of all patients randomized, number ineligible, early termination due to AE/SAE, the number of subjects with an SAE, deaths, dropout for other reasons, and the number of subjects lost to follow-up. Additional summaries will include reasons for patients discontinuing treatment and/or modifying treatment dosages, and a summary of patients' treatment status. A listing of screened and ineligible patients along with the reason for each also will be summarized (Tables 9.4 - 9.7 in Section 9, Appendices).

### **5.3.3 Analytic Methods for Time-to Event Data**

The analytic method for the primary analysis will be a time-to-event analysis using the log-rank test, as previously described. Cox proportional hazards regression models will be used for secondary assessments[5]. Graphical analyses (log-minus-log plots) will be used to check the assumption of constant hazard ratios.

For the primary analysis, two 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[6]. Additional analyses involving the overall 3-treatment group comparison, and use of additional study populations (see Section 4) for 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. Generally, a patient will be considered a treatment failure if for any reason, the endpoint determination cannot be made per the pre-specified study requirements. The time to this imputed event will be from randomization to the last recorded patient visit. See Section 5.3.6 below for further details of handling missing data. A patient who is lost to follow-up for reasons deemed unrelated to his or her endpoint status will be treated as a censored observation as of the last patient visit. If a patient does not have a FAP related event at the 24 month close-out visit, the patient will be treated as a censored observation as of the actual follow-up time for the close-out visit.

### **5.3.4 Analytic Methods for Categorical or Continuous-Valued Secondary Outcome and Safety Data**

For categorical data, comparisons will be made between treatment groups using standard chi-squared techniques as the primary approach. In particular, the 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[7].

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[3].

### **5.3.5 Assessment of Toxicities**

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). 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) will also be tabulated separately. Tables that enumerate adverse events by severity will 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 (Tables 9.8 - 9.17 in Section 9, Appendices) using the above-mentioned methods for analysis of categorical data.

### **5.3.6 General Procedures for Handling 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. A patient will be considered a treatment failure if for any reason, the endpoint determination cannot be made per the pre-specified protocol. The time to this imputed event will be from randomization to the last

recorded patient visit. Any secondary or sensitivity analysis that includes this assumption will be clearly noted. Similarly, any sensitivity analysis that incorporates the last observation carried forward (LOCF) method, to compensate for early patient dropouts or missing data, will be clearly noted.

Secondary analysis data include the presence of a specific genetic mutation, and urinary metabolite concentrations (see Section 3.2.2). The primary analysis of the secondary objectives will include collected data only, without imputing or weighting data to compensate for missing data. 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 (September, 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. These procedures will be fully described in the study report.

### **5.3.7 Subgroup Analyses**

Subgroups will be analyzed in the spirit of exploratory analyses including but not limited to the various study populations (see Section 4) and separately within each disease-prognosis stratum.

## **5.4 Health Related Quality of Life (HRQoL) Statistical Methods**

For this study four (4) instruments to measure HRQoL and patient preferences or utilities will be administered to subjects at baseline and at 3, 6, 12, 18, and 24 months post-enrollment/end of treatment. 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[8] 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[9] 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[10, 11]. It provides a simple descriptive profile and a single index value for health status.
- The Cancer Worry Scale[12] 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. 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[10, 11]. 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*[12].

This trial has three strata and three treatment options with 150 patients to be entered. 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.

## 5.5 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[13, 14]. Data from the FFQ will be analyzed using a polyamine database[15] 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, 12 months and 24 months/end of treatment for subjects at North American (U.S. and Canada) sites only. Clinical study sites outside of North America will not be included because the foods on the North American food frequency questionnaire not the same as those widely consumed in Europe and elsewhere. The results of the FFQ will be used to corroborate results from another recent trial[16] 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.*[17] could lead to dietary restrictions in combination with the combined eflornithine-sulindac therapy.

## **6. RANDOMIZATION ALGORITHM AND STRATIFICATION FACTORS**

A total of 150 eligible patients will be enrolled in this study. Patients 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 patient 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.

## **7. OTHER ISSUES AND FURTHER DETAILS**

### **7.1 Statistical Software Used in Data Analysis**

All analyses will be performed using SAS statistical analysis software version 9.1 or later. If other software is used (i.e. WinNonPop for population pharmacokinetics, SAS macros for futility analysis, etc.), it will be clearly described in the clinical and statistical study reports.

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## **9. APPENDICES**

### **9.1 Appendix: Sample Study Clinical Report Tables**

**Table 9.1 - Registration by Institution****Registrations ending XX/XX/20XX**

Institutions	Total Reg	Institutions	Total Reg
Institution 1	##	Institution 3	##
Institution 2	##	Total	##

**Table 9.2 - Patient Demographics****Registrations ending XX/XX/20XX**

	Total (n=##)		Total (n=##)
AGE		HISPANIC	
Median	##.#	Unknown	## ##%
Minimum	##.#		
Maximum	##.#	RACE	
		White	## ##%
SEX		Black	## ##%
Males	## ##%	Native American	## ##%
Females	## ##%		

**Table 9.3 - Patient Characteristics, Overall and by Marginal Arm**

Characteristic	Overall (n/N (%))	Arm 1 (n/N (%))	Arm 2 (n/N (%))	Arm 3 (n/N (%))	Overall P-value
Factor 1	n/N (%)	n/N (%)	n/N (%)	n/N (%)	#####
Factor 2	n/N (%)	n/N (%)	n/N (%)	n/N (%)	#####
Factor 3	n/N (%)	n/N (%)	n/N (%)	n/N (%)	#####

**Table 9.4 - Summary of Treatment Status**

Reason Off Treatment	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Death				
On Treatment				
Progression				
Pt pref, not toxicity				
Med req, toxicity				
Treat completed per protocol				

**Table 9.5 - Summary of Treatment Status and Eligibility**

	Eligibility			
Treatment Status (Reason off Tx)	Ineligible, Exception	No	Yes	Total
Death				
On Treatment				
Progression				
Pt pref, not toxicity				
Med req, toxicity				
Treat completed per protocol				
<i>Total</i>				

**Table 9.6 - Listing of Patients Off Treatment Due to Toxicity**

Patient	Drug (Placebo / CPP-1X / Sulindac)	Explanation/Comments

**Table 9.7 – Drugs/Dose Interrupted or Discontinued While on Study**

Drug (CPP-1X, Sulindac)		
Action	Count	Percent
None		
Dose Interrupted		
Discontinued Drug		

**Table 9.8 - Listing of Treatment-Emergent Serious Adverse Events**

Patient	Start Date	Stop Date	Adverse Event	Severity	Action Taken	Attributable to Study Drug

**Table 9.9 - Treatment-Related Treatment-Emergent Adverse Events Grade 3 or Higher by Organ System**

System	Adverse Event	Count	% of Treated Patients by treatment group
Allergy/immunology			
Blood/Bone Marrow			

**Table 9.10 - All Treatment-Emergent Adverse Events Grade 3 or Higher by Organ System**

System	Adverse Event	Count	% of Treated Patients by Treatment Group
Allergy/immunology			
Blood/Bone Marrow			

**Table 9.11 – Treatment-Related Treatment-Emergent Adverse Events by Organ System**

System	Adverse Event	Count	% of Treated Patients by Treatment Group
Allergy/immunology			
Blood/Bone Marrow			

**Table 9.12 - All Treatment-Emergent Adverse Events by Organ System**

System	Adverse Event	Count	% of Treated Patients by Treatment Group
Allergy/immunology			
Blood/Bone Marrow			

**Table 9.13 - Treatment-Related Treatment-Emergent Adverse Events by Frequency of Occurrence**

Adverse Event	Count	% of Treated Patients
Adverse Event 1		
Adverse Event 2		

**Table 9.14 - All Treatment-Emergent Adverse Events by Frequency of Occurrence**

Adverse Event	Count	% of Treated Patients
Adverse Event 1		
Adverse Event 2		

**Table 9.15 - Treatment-Emergent Adverse Events Attributable to Treatment**

	Toxicity Degree											
	Grade 0		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
Adverse Event	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Adverse Event 1	##	(##%)	##	(##%)	##	(##%)	##	(##%)	##	(##%)	##	(##%)

**Table 9.16 - Treatment-Emergent All Adverse Events**

	Toxicity Degree											
	Grade 0		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
Adverse Event	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Adverse Event 1	##	(##%)	##	(##%)	##	(##%)	##	(##%)	##	(##%)	##	(##%)

**Table 9.17 - Listing of All Study Patient Deaths**

Patient Number	Off Study Date	Date of Last Treatment	Date of Death	Days from Last Treatment to Death

## **STATISTICAL ANALYSIS PLAN**

### **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)**

Protocol Number: CPP FAP-310

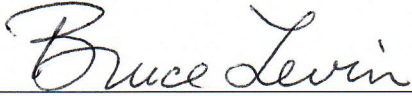
Statistical Analysis Plan

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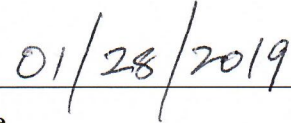
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**STATISTICAL ANALYSIS PLAN (SAP) SIGNATURE SHEET**

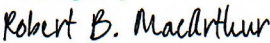
The undersigned have reviewed the format and content of this Statistical Analysis Plan (SAP) for Cancer Prevention Pharmaceuticals, Inc. study CPP FAP-310 titled “A DOUBLE-BLIND, RANDOMIZED, PHASE III TRIAL OF THE SAFETY AND EFFICACY OF CPP-1X/SULINDAC COMPARED WITH CPP-1X, SULINDAC AS SINGLE AGENTS IN PATIENTS WITH FAMILIAL ADENOMATOUS POLYPOSIS (FAP)” and have approved this SAP as finalized.



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## 1. LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
ANCOVA	Analysis of covariance
CPP	Cancer Prevention Pharmaceuticals, Inc.
CPP-1X	Eflornithine, DFMO, Difluoromethylornithine
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DMC/DSMB	Data Monitoring Committee/Data Safety Monitoring Board
EDC	Electronic Data Capture System
EFS	Event-Free Survival
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
FAP	Familial Adenomatous Polyposis
FDA	Food and Drug Administration
FFQ	Food Frequency Questionnaire
HRQoL	Health Related Quality of Life
ICH	International Conference on Harmonization
ITT	Intent-To-Treat
LGI	Lower Gastrointestinal
LGIOI	LGI Observed Improvement
LOCF	Last Observation Carried Forward
NASR	Nutrition Assessment Shared Resource (Fred Hutchinson Cancer Research Center)
NCI	National Cancer Institute
ODC	Ornithine Decarboxylase
QLQ	Quality of Life Questionnaire
SAM	S-Adenosyl Methionine
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
UGI	Upper Gastrointestinal
UGIOI	UGI Observed Improvement
Z-score	The value of the critical ratio (score statistic divided by its standard error) based on the stratified log-rank statistic.

## **2. INTRODUCTION**

This Statistical Analysis Plan (SAP) describes the proposed statistical analysis of the Cancer Prevention Pharmaceuticals, Inc. (CPP) study CPP FAP-310 entitled: “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)”.

The purpose of this document is to apply sound analytic principles through description and pre-specification of the statistical approaches and data handling conventions for key analyses and the randomization processes.

This plan will focus on analysis of the primary and secondary endpoints, intended to assess the extent to which the combination treatment (CPP-1X 750 mg daily + sulindac 150 mg daily) is more effective than each of the two single agent treatments alone (CPP-1X 750 mg daily + placebo, and sulindac 150 mg daily + placebo) in delaying the time from the date of randomization to the date of the first occurrence of any FAP-related event in FAP patients. Sample size and total FAP-related events will be discussed, along with study population definitions. In addition, we will summarize our approach regarding the analysis of safety data, pharmacokinetic data, and patient reported quality of life data. The composition, charter, and initial tasks of the Data Monitoring Committee (DMC) will be described, along with planned interim analyses.

## **3. STUDY OBJECTIVES AND ENDPOINTS**

### **3.1 Overview of Study**

This is a randomized, double-blind, phase III trial in patients with FAP to evaluate the safety and efficacy of the combination product 750 mg CPP-1X + 150 mg sulindac versus each of the two single-agent products: 1) 750 mg CPP-1X; and 2) 150 mg sulindac. The primary study comparisons will be made between the combination product and each single agent product, separately.

Eligible patients who have given informed consent will enter the study with the intent to participate for the full treatment period of 24 months. Based on a subject's date of randomization, patients will be offered continued preparticipation in blinded treatment for up to a total of 36, 42 or 48 months of treatment if they have completed the initial 24 months of treatment without an FAP event until one of the following occurs: 1) subject has an FAP event or comes off study for other reasons, 2) all randomized subjects have reached a minimum of 24, 36, 42 or 48 months of treatment.

A stratified randomization procedure will be used 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 patient as a whole. In order to minimize potential treatment arm imbalance a centralized randomization process will be used to balance treatment groups within disease prognostic strata.

The stratification is predicated on the following projected event rates for the disease site specific eligibility criteria (rectal/pouch polyposis, duodenal polyposis, pre-colectomy) which are provided in the clinical study protocol (Appendix E) and summarized in Table 3.1.

**Table 3.1 Projected Event Free Rate by Disease Site**

Disease Site	Projected 2-year Event Free Rate Without Treatment
Rectum/Pouch Polyposis	Excisional intervention and/or high risk adenoma – 40 - 60%
Duodenal Polyposis	Excisional intervention, Spigelman stage progression, cancer – 50%
Pre-colectomy	Colectomy, proctocolectomy – 10%

The stratified randomization will be reflected in stratified analyses for the primary and secondary endpoints. For design purposes only, however, the following simplified assumptions were made: an overall event free proportion of 30% in the single agent treatment group and 60% in the combination treatment group after 24 months of study treatment. This is described further in Table 3.2 below. See Section 5.1 for sample size and power calculations.

**Table 3.2 Overall Event Free Proportions After Two Years of Follow-up\***

Treatment	S(t)	t (months)	Median Time to Event (months)
Combination	0.6	24	32.566
Single Agent	0.3	24	13.817

\*These proportions are assumed for design purposes only. The median times to event are based on the assumption of an exponential time-to-event function S(t) in each group.

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 above 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 patients nor Investigator nor Sponsor will be aware of treatment assignment.

The grading of adverse events will be based on the current version of the NCI Common Terminology Criteria for Adverse Events (CTCAE Version 4.03).

Refer to the CPP FAP-310 protocol for the details of the treatment and study schedule, and description of study procedures and tests.

### 3.2 Study Objectives

The primary study analysis will be performed using the intent-to-treat (ITT) population which is defined in Section 4.1. Statistical methods for the primary analysis are described in Sections 5.1 and 5.5.3.

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 time from the date of randomization to the date to the first occurrence of any FAP-related event.

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 Section 3.2.1 below, the decision to seek regulatory approval based upon the results of the primary objective will be taken sequentially.

### **3.2.1 Primary Analysis**

The primary analysis will be a time-to-event analysis using the stratified log-rank test. Graphical analyses (log-minus-log plots) will be used to check the assumption of constant hazard ratios with the COX model. See Section 7.3 below for further details of the calculation of the stratified log-rank statistic. The strata are the patient's sites of disease involvement at baseline, which is determined prior to randomization, and are: Rectal/pouch polyposis, Duodenal polyposis, and Pre-colectomy.

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[8]. Additional analyses involving the overall 3-treatment group comparison and use of additional study populations (see Section 4.) for the two pairwise treatment comparisons, will be performed as supplemental analyses. Refer to section 5.5.3 for further details.

### **3.2.2 Regulatory Review of Primary Outcome Compliance**

CPP has received advice from both the FDA and the EMA concerning the test method and criteria (Sections 3.2 and 5.) to be used when analyzing the primary study outcome, including the value of alpha.

The US Food and Drug Administration (FDA) noted that the comparison of single agent CPP-1X vs. combination treatment will not provide information about the treatment effect of CPP-1X (i.e. eflornithine), and therefore this result will not be included in the product label. Therefore, the primary analysis of import to FDA is the comparison of single agent sulindac vs. combination treatment.

The European Medicines Agency (EMA) noted that for the three arm trial design the superiority of the combination treatment must be tested against both mono-components. The combination treatment must be shown to be superior to both mono-components, or else the results will be considered inconclusive. As a consequence, consistent with EMA/SAWP commentary, alpha does not need to be adjusted for multiplicity and two separate 5% two-sided tests will suffice.

To harmonize the advice provided by these two Agencies, 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.

### 3.2.3 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.

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). Here are the specific possibilities (where “Improvement” stands for either the UGIOI or LGIOI secondary endpoint):

- If the 6-month score is –2 or –1, Improvement=NO irrespective of the 12-month score.
- If the 6-month score is 0, then Improvement=YES if and only if the 12-month score is +1 or +2. Otherwise Improvement=NO.
- If the 6-month score is +1 or +2, then Improvement=YES if and only if the 12-month score is greater than or equal to 0. Otherwise Improvement=NO.

Any patient who drops out of the study before the month 12 assessment will be considered Improvement=NO.

These binary UGIOI and LGIOI secondary efficacy endpoints will be compared in a manner analogous to the primary analysis, using the same two primary 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), and conditioning on the three disease site strata (Rectum/Pouch Polyposis, Duodenal Polyposis, Pre-colectomy). The null hypothesis of no association between treatment group and Improvement endpoints will be tested using the exact Mantel-Haenszel procedure for combining the evidence contained in the fourfold tables (Treatment=Single agent vs. Combination cross-classified by Improvement=YES vs. NO) across the three strata. For each of the two treatment comparisons, exact Mantel-Haenszel p-values will be calculated for both the UGI and LGI assessments (using the point-probability method based

on the convolution of three independent central hypergeometric distributions; see [1]).

The overall type I error for the secondary efficacy analysis will be controlled using the Hochberg step-up method for multiple comparisons[2]. This analysis will be performed in the ITT population. The primary analysis will serve as a gatekeeper to control the overall type I error rate at 0.05 for both primary and secondary analyses. That is, significance for the secondary efficacy analysis will be declared only if the primary p-value is 0.05 or less, when the p-values are tested sequentially per the Hochberg method[2].

Further analyses of the secondary endpoints may be conducted to evaluate and provide additional evidence to support its validity and confirm its clinical relevance.

### 3.2.4 Other Secondary Outcomes

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 Section 4 Populations for Analysis) 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 (see below).

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 (see below). The subcategories of FAP events include:

**Table 3.3 Disease Site Subgroups**

No	Group	Description
1	Disease Progression Indicating Need for Colectomy with IRA or Total Procto-Colectomy	Applies only to subjects with FAP surgical status of pre colectomy (field name: DIAGSXST, code 1)
2	Excisional intervention by surgical snare or trans-anal excision to remove any polyp $\geq 10$ mm in size (per pathology report) and/or pathologic evidence of high grade dysplasia	Excisional intervention does not apply to subjects with FAP surgical status of colectomy with ileostomy (field name: DIAGSXST, code 4) or subjects with FAP surgical status of pre colectomy (field name: DIAGSXST, code 1). For all remaining subjects, all $>5$ mm polyps must have been removed at baseline  also

No	Group	Description
		High grade dysplasia does not apply to subjects with FAP surgical status of colectomy with ileostomy (field name: DIAGSXST, code 4)
3	Disease Progression Indicating Need for Proctectomy	Does not apply to subjects with FAP surgical status of proctocolectomy with ileal pouch anastomosis (IPAA) (field name: DIAGSXST, code 3) or FAP surgical status of colectomy with ileostomy (field name: DIAGSXST, code 4)
4	Disease Progression Indicating Need for Pouch resection	Does not apply to subjects with FAP surgical status of pre colectomy (field name: DIAGSXST, code 1). or FAP surgical status of colectomy with ileostomy (field name: DIAGSXST, code 4) or FAP surgical status of colectomy with ileorectal anastomosis (IRA) (field name: DIAGSXST, code 2)
5	Development of cancer in rectum or pouch	Does not apply to subjects with FAP surgical status of colectomy with ileostomy (field name: DIAGSXST, code 4)
6	Progression in Spigelman Stage to more advanced stage (Stage 2, 3, 4)	Does not apply to subjects without duodenum (determined by abdominal surgical procedure of duodenectomy, duodenohepatojejunostomy, or Whipple procedure (field name SXPROC) and screening/baseline upper GI endoscopy not done (field name UGIND, Boolean data type)
7	Disease Progression indicating need for excisional intervention (sub-mucosal resection, trans-duodenal excision, duodenectomy, ampullectomy, Whipple procedure)	Does not apply to subjects without duodenum (determined by abdominal surgical procedure of duodenectomy, duodenohepatojejunostomy, or Whipple procedure (field name SXPROC) and screening/baseline upper GI endoscopy not done (field name UGIND, Boolean data type)
8	Development of cancer in duodenum	Does not apply to subjects without duodenum (determined by abdominal surgical procedure of duodenectomy, duodenohepatojejunostomy, or Whipple procedure (field name SXPROC) and screening/baseline upper GI endoscopy not done (field name UGIND, Boolean data type)
9	Spigelman stage (no progression)	Does not apply to subjects without duodenum (determined by abdominal surgical procedure of duodenectomy, duodenohepatojejunostomy, or Whipple procedure (field name SXPROC) and

No	Group	Description
		screening/baseline upper GI endoscopy not done (field name UGIND, Boolean data type)
10	>= 10 mm polyp in rectum pouch	Does not apply to subjects with FAP surgical status of colectomy with ileostomy (field name: DIAGSXST, code 4) or subjects with FAP surgical status of pre colectomy (field name: DIAGSXST, code 1). For all remaining subjects, all >5 mm polyps must have been removed at baseline.
11	High grade dysplasia (rectum-pouch)	Does not apply to subjects with FAP surgical status of colectomy with ileostomy (field name: DIAGSXST, code 4)

These subcategories will be analyzed within the assigned disease strata (i.e. assigned at time of randomization). Separately, they will be analyzed by Disease Site, according to the concept of “the patient as a whole” meaning that *all known disease sites will be considered* because patients more often than not have more than one diseased organ system. For example, a patient randomized to treatment in the Duodenal Polyposis stratum who is also known to have colonic polyps will appear in the analyses for both Disease Site subgroups (Duodenal and Colonic). The total number of patients in the Duodenal Disease Site subgroup will include, for example, all patients randomized in the Duodenal Polyposis stratum + all other patients with known duodenal disease (irrespective of whether they have rectal/pouch disease). A similar approach will be taken for the Rectum/Pouch Polyposis group and Pre-colectomy strata.

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 (see Section 5.6 Health Related Quality of Life (HRQoL) Statistical Methods 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 (see Section 5.7 Dietary Assessment) and related to treatment group and study outcomes.

Safety outcome data and analyses are described in Section 5.5.5 Assessment of Toxicities.

## 4. POPULATIONS FOR ANALYSIS

### 4.1 Intent-to-Treat (ITT) Population

The intent-to-treat population includes all patients that have been randomized to one of the three study arms. Patients 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.

#### **4.2 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 according to which actual treatment was initially received.

#### **4.3 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.

#### **4.4 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:

- Patients 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.

### **5. DETERMINATION OF SAMPLE SIZE AND STATISTICAL METHODS**

#### **5.1 Determination of Sample Size**

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 protocol 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.

#### **5.2 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 (see section 7.3 for details);
- 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. This is described further in Table 3.2.

### 5.3 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. Note that the primary analysis described below, in Section 7.3, does not rely on such an assumption and provides a statistically valid test of the null hypothesis even if hazard rates are not constant. 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  $0.30 = \{\log(0.70) / \log(0.30)\}$  (see discussion below).

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 [3, 4]. 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.

#### **5.4 Data Monitoring Committee (DMC) DMC General Information**

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. 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 efficacy and 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 an 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.

##### **5.4.2 Prespecified Interim Efficacy and Futility Analysis**

A pre-specified interim efficacy and futility analysis will be conducted as described below. 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. After reviewing the analysis results in a closed session, the DMC will provide recommendations regarding possible termination of the study for either futility, efficacy, or safety reasons, to the Sponsor Steering Committee.

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.

As stated above in Section 3.2, the combination of CPP-1X active + sulindac active is specified as the reference treatment group because it is common to both comparisons and 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.

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.

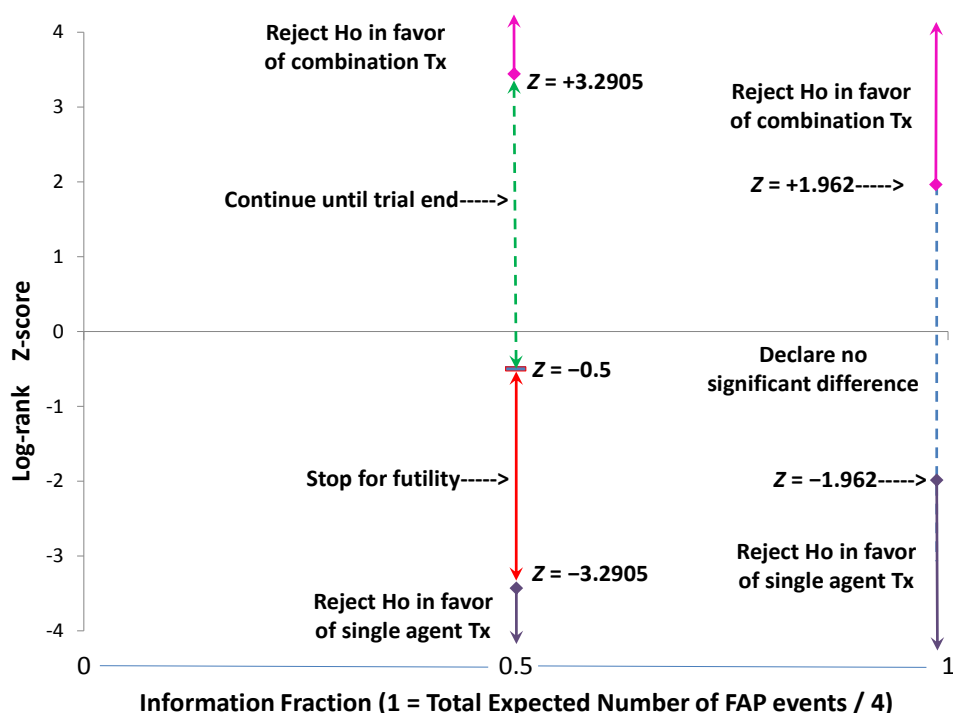
The details of the efficacy and futility analysis are provided in Table 5.1 below which presents a schematic diagram of the procedure. Also Table 5.2 provides more precise conditional power values corresponding to the futility criterion  $Z = -0.50$  as a function of the total number of events in either two-arm comparison. See Section 7.4 below for further details of the conditional power calculation.

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.

**Table 5.1 Interim Futility Analysis Details**

Estimated Look Time Point	Description
<p>When 45 primary endpoints have occurred, corresponding to when 50% of maximum trial information has been amassed</p>	<p>Efficacy criterion <math>Z = 1.962</math> at terminal analysis.  Futility criterion of <math>Z = -0.50</math> or less at interim analysis.  Type I error for exiting the upper efficacy boundary at or before terminal analysis = 0.024952.*  Type I error for exiting the lower efficacy boundary at or before terminal analysis = 0.001928.*  Total Type I error for end of study comparison = 0.026936.*  Assuming 52 events at trial end in either two-arm comparison, power = 0.8705.  Assuming 55 events at trial end in either two-arm comparison, power = 0.8881.</p>
<p>*Assume one interim analysis at <math>\frac{1}{2}</math> information time with upper efficacy boundary at <math>B_e = 3.2905</math>, lower efficacy boundary at <math>-B_e</math>, and one-sided futility boundary <math>B_f = -0.50</math>. Assume upper efficacy terminal criterion <math>C = 1.9602</math> and lower efficacy terminal criterion <math>-C</math>. Then the probability of exiting the upper efficacy boundary at either interim or terminal analysis under the null hypothesis is given by</p> $\Phi(-B_e) + \int_{B_f}^{B_e} \Phi(z - C\sqrt{2})\varphi(z)dz$ <p>and the probability of exiting the lower efficacy boundary at either interim or terminal analysis under the null hypothesis is given by</p> $\Phi(-B_e) + \int_{B_f}^{B_e} \Phi(-z - C\sqrt{2})\varphi(z)dz,$ <p>where <math>\varphi(z)</math> is the standard normal probability density function and <math>\Phi(z)</math> is the standard normal cumulative distribution function.</p>	

**Figure 5.1 Schematic Diagram for Efficacy, Futility, and Terminal Analyses**



**Table 5.2 Conditional Power at the Futility Boundary as a Function of Number of FAP Events at the Time of Futility Analysis, Using Futility Criterion  $Z = -0.5$**

Total FAP events in either two-arm comparison at time of futility analysis	Assumed number of FAP-related events in either two-arm comparison at trial conclusion	Conditional power
30	60	0.177
29	58	0.167
28	56	0.157
27	54	0.148
26	52	0.138
25	50	0.129
24	48	0.120
23	46	0.111
22	44	0.103

## 5.5 Statistical Methods

### 5.5.1 Demographic and Baseline Characteristics

Patients in the three populations (see Section 4.) 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)[5]. 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.

### **5.5.2 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.

Patient disposition and treatment will be summarized for the ITT and safety populations defined previously (see Section 4.2). Patient disposition will be consistent with the CONSORT criteria[6], 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 for more than 90 days from randomization to month 36 or more than 105 days from randomization to month 42 or more than 120 days from randomization to month 48, 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.

### **5.5.3 Analytic Methods for Time-to-Event Data**

The analytic method for the primary analysis will be a time-to-event analysis using the stratified log-rank test, as previously described. The stratified Cox proportional hazards regression models will be used for secondary assessments[7]. Graphical analyses (log-minus-log plots) will be used to check the assumption of constant hazard ratios. See Section 7.3 below for further details of the calculation of the stratified log-rank statistic.

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[8]. Additional analyses involving the overall 3-treatment group comparison, and use of additional study populations (see Section 4.) for 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.

If a subject has two or more missing assessments, time to first FAP-related event for the subject will be censored at the time of last adequate evaluation prior to the missing assessment.

If a subject has no baseline assessment, time to first FAP-related event for the subject will be censored at the date of randomization.

See Section 5.5.6 below for further details of handling missing data. Every effort will be made to minimize the occurrence of censoring and missing data.

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 aid in the interpretation of the primary result.

#### **5.5.4 Analytic Methods for Categorical or Continuous-Valued Secondary Outcome and Safety Data**

For categorical data, comparisons will be made between treatment groups using standard chi-squared techniques as the primary approach. In particular, the 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[1].

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 polypsis, 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[5].

#### **5.5.5 Assessment of Toxicities**

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) will also be tabulated separately. Tables that enumerate adverse events by severity will 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.

### 5.5.6 General Procedures for Handling 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 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 3.2.3). 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. These procedures will be fully described in the study report.

### 5.5.7 Subgroup Analyses

Subgroups will be analyzed in the spirit of exploratory analyses including but not limited to the various study populations (see Section 4) and separately within each disease-prognosis stratum.

## 5.6 Health Related Quality of Life (HRQoL) Statistical Methods

For this study four (4) instruments to measure HRQoL and patient preferences or utilities will be administered to subjects at baseline and at 3, 6, 12, 18, 24, 30, 36, 42 and 48 months post-enrollment/end of treatment. 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[9] 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[10] 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[11, 12]. It provides a simple descriptive profile and a single index value for health status.

- The Cancer Worry Scale[13] 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. 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[11, 12]. 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*[13].

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.

## **5.7 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[14, 15]. Data from the FFQ will be analyzed using a polyamine database[16-18] 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. Clinical study sites outside of North America will not be included because the foods on the North American food frequency questionnaire are not the same as those widely consumed in Europe and elsewhere.

## 6. RANDOMIZATION ALGORITHM AND STRATIFICATION FACTORS

At least 150 eligible patients will be randomized in this study. Patients 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 patient 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.

## 7. OTHER ISSUES AND FURTHER DETAILS

### 7.1 Statistical Software Used in Data Analysis

All analyses will be performed using SAS statistical analysis software version 9.1 or later. If other software is used (i.e. WinNonPop for population pharmacokinetics, SAS macros for futility analysis, etc.), it will be clearly described in the clinical and statistical study reports.

### 7.2 Draft Tables, Listings and Figures

The TLF (Tables, Listings, Figures) templates and shells are noted as Ver. 2.0, October 6, 2014 (SAP Ver. 3.0 September 30, 2014) based on revision provided from Data Management/Statistical Group at Ockham now Chiltern. These draft templates have been removed as an Appendix to the amended SAP and are available upon request.

### 7.3 Details of Calculating the Stratified Log-rank Z-Score

Patient follow-up will be analyzed in continuous time, although it is recognized that FAP event detection will cluster around scheduled study visits, at months 6, 12, 18, 24, 30, 36, 42 and 48 and event times may be tied as follow-up time is measured only to the nearest day. Censorings are possible at the baseline visit (month 0) for patients who dropped out of the trial before their first follow-up visit. The primary test statistic will be the stratified log-rank statistic. Each two-arm comparison will be performed separately. This will be implemented in SAS by specifying the TIES=DISCRETE option in PROC PHREG. The single agent treatments, respectively, will be coded as 1 and the combination treatment will be coded as 0. The square root of the score test chi-squared statistic will be calculated and the *sign* of the estimated log hazard ratio (+ if the HR>1 and – if the HR<1) will be attached. This results in the stratified log-rank Z-score. In symbols,  $Z_k = \text{sign}(\hat{\beta}) \times \sqrt{X^2}$ , where  $\hat{\beta}$  denotes the estimated log hazard ratio coefficient for treatment *A* in the Cox model and where  $X^2$  denotes the SCORE TEST chi-squared statistic reported within the “Testing Global Null Hypothesis: BETA=0” table at the top of the PHREG results section.

The following sample PHREG procedure could be used in SAS to derive the stratified log-rank Z-score:

```
proc phreg data=TwoArmData;  
model time*censor(1) = Treatment / rl ties=discrete;
```

```
strata Stratification_Factor;  
title "Stratified Cox Regression Analysis for Single Agent vs Combination";  
run;  
quit;
```

NB: The model includes the variables time, censor, and treatment, only.

#### 7.4 Details of Calculating Conditional Power

Conditional power is given by the following formula[20].

$$\text{Conditional power} = \Phi \left( \frac{Z_k \sqrt{I_k} - z_{1-\alpha/2} \sqrt{I_K} + \theta(I_K - I_k)}{\sqrt{I_K - I_k}} \right),$$

where

$Z_k$  is the value of the stratified log-rank test statistic from the observed data at interim analysis;  
 $z_{1-\alpha/2}$  is the critical value for a two-tailed test at  $\alpha=0.05$ , namely +1.962 adjusted for the interim efficacy analysis;

$I_K$  = the information number expected at trial end =  $\frac{1}{4}$  times the total expected number of events;

$I_k$  = the information number at futility analysis =  $\frac{1}{4}$  times the observed number of events at interim analysis;

$\theta$  is the log hazard ratio at the design alternative,  $\log 2.3569 = -\log 0.42428 = +0.85736$ ; and

$\Phi(\cdot)$  is the standard normal cumulative distribution function.

Example. Suppose at the time of interim analysis, the number of FAP-related events are as follows: For single-agent treatment A, 20; for single-agent treatment B, 16; and for combination treatment C, 9. Then in the two-arm comparison of A versus C, there would be a total of 29 events, so the information number is  $I_k=29/4=7.25$ . We assume that there will be double this number for the corresponding comparison at the end of the trial; thus  $I_K = 14.5$ . Suppose the Z-score at the futility analysis happens to just equal the futility criterion, i.e., suppose  $Z_k = -0.50$ . Then applying the above formula yields conditional power of

$$\Phi \left( \frac{-0.5\sqrt{7.25} - 1.962\sqrt{14.5} + 0.85736(14.5 - 7.25)}{\sqrt{14.5 - 7.25}} \right) = 0.1670.$$

This is the conditional power *at the futility boundary*. Suppose, however, that the observed Z-score at the futility analysis were actually +0.50 instead of -0.5. Then the -0.5 in the first term of the above expression would be replaced by  $Z_k=+0.50$ , and the resulting *observed* conditional power would be 0.5135, a non-futile result.

Note that the probability of a significant *negative* result at the terminal analysis, given that there is no stopping for futility at the interim analysis, is not included in the above expression. That is because practical interest for futility analysis resides only in the conditional probability of a significant benefit of the combination treatment. In any case, the term which has been omitted is numerically negligible.

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**Study ID: CPP FAP-310, 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)**

**Summary of SAP Changes Ver. 2.0 11April2013 to Ver. 3.0 30September2014**

Section	Change or Revision
<b>Global Changes</b>	Changed version to Ver. 3.0 September 30, 2014, corrected typographical errors, updated TOC
<b>3.2 Study Objectives and Primary Hypothesis Testing</b>	Clarified report sections where the study analysis and ITT population are defined, as follows: “The primary study analysis will be performed using the intent-to-treat (ITT) population which is defined in Section 4.1. Statistical methods for the primary analysis are described in Section 5.1”
<b>5.1 Determination of Sample Size, #1</b>	Reiterated (i.e. was stated elsewhere in the document) that, “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, for each of the two between-group comparisons (i.e. CPP-1X plus sulindac vs. CPP-1X and CPP-1X plus sulindac vs. sulindac);”
<b>5.2 Data Monitoring Committee</b>	Clarified the futility analysis: “The futility assessment will be performed in a blinded A versus B manner” and add the following section:  For the futility interim analysis, the futility stopping criterion of $Z=0.50$ is one-sided, and corresponds to a conditional power criterion of approximately 0.12 (to two decimals). That is, assuming between 52 and 55 expected total number of events by trial end, 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, then under the design alternative hazard ratio of 0.4243, there would be only a 12% probability (or less) 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 the trial for futility. Futility analysis results will be presented in a simple manner where the DMC will be informed that the conditions indicating futility have been met.
<b>5.3.3 Analytic Methods for Time-to Event Data</b>	Clarified that both the log rank test and the Cox proportional hazards regression models will be <i>stratified</i> .
<b>Appendix</b>	Updated all of the Sample Study Clinical Report Tables.
<b>END</b>	

**Study ID: CPP FAP-310, 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)**

**Summary of SAP Changes Ver. 3.0, 30September2014 to Ver. 4.0, 15February2016**

Section	Change or Revision
<b>Global Changes</b>	<b>Changed</b> version to Ver. 4.0 February 15, 2016; updated TOC, updated references
<b>Section 1. List of Abbreviations</b>	<b>Added</b> AC – Adjudication Committee; CRO – Contract Research Organization; EDC – Electronic Data Capture
<b>Section 3.1, Overview of Study</b>	<p><b>Added</b> to 2<sup>nd</sup> paragraph:</p> <p>Subjects completing 24 months of treatment without an FAP event may continue treatment for up to 12 additional months until one of the following occurs: 1) subject has an FAP event or comes off study for other reasons, 2) all randomized subjects have reached a minimum of 24 months of treatment or have come off study prior to reaching 24 months of treatment.</p> <p><b>Deleted</b> Accrual is expected to take 6 – 12 months.</p> <p>Paragraph 4, <b>Changed</b> Appendix D to Appendix E</p> <p><b>Updated</b> CTCAE version from Version 4 to Version 4.03</p>
<b>Section 3.2 Study Objectives and Primary Hypothesis Testing</b>	1 <sup>st</sup> paragraph, <b>Inserted</b> “Section” in front of 5.1
<b>Section 3.2.1 Regulatory Review of Primary Outcome Compliance</b>	<b>Changed</b> SWAP to SAWP
<b>Section 4.3 Per Protocol Population</b>	<p><b>Changed</b> “The per protocol population is defined as the subset of the ITT population who completed all 24 months of treatment and have primary endpoint determination performed per protocol specifications.”</p> <p><b>To</b> “The per-protocol population is defined as the subset of the ITT population that fulfill all protocol eligibility, intervention, and outcome assessments.”</p>
<b>Section 4.4 Other Populations</b>	<p><b>Revised</b> the first paragraph to read:</p> <p>Within the entire study patient population there will be subsets who did not receive the full course of per protocol treatment. The patient diary and pill count will define the extent of compliance. This subgroup of patients will be categorized into various cohorts. For consistency, an adjudication committee will be established, to review all study events (i.e. FAP related events and dropouts), and categorize them either as censored observations or imputed endpoints (see Section 5.2.2). For exploratory and sensitivity analysis the following dropout subsets will be included in secondary analyses:</p>
<b>Section 5.2</b>	<b>Changed</b> section title to Data Monitoring Committee (DMC) and Adjudication Committee (AC)
<b>Section 5.2.1 Data Monitoring Committee (DMC)</b>	<p>2<sup>nd</sup> paragraph, <b>Changed</b> “...document to FDA” to “document to FDA and EMA”</p> <p>3<sup>rd</sup> paragraph, <b>Deleted</b> “(based on a blinded A/B comparison).”</p> <p>4<sup>th</sup> paragraph</p> <p>3<sup>rd</sup> sentence <b>changed</b> “perform an assessment of” to “assess”</p> <p>5<sup>th</sup> sentence <b>added</b>....study statistician will, “if possible”, estimate the overall....</p> <p>7<sup>th</sup> sentence <b>deleted</b> “With this approach study enrollment can continue uninterrupted at the study sites, if it is decided to increase study sample size.” <b>Replaced text</b> with the following “If this type of assessment is not possible, then an 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.”</p> <p>5<sup>th</sup> paragraph: <b>revised</b> as follows:</p>

Section	Change or Revision
	<p>The futility assessment will be performed after a total of 45 adjudicated primary endpoints have occurred, which represents 50% of expected maximum trial information, or as soon thereafter as possible.</p> <p>The futility analysis will be performed for each of the two treatment comparisons contained in the primary objective:</p> <ol style="list-style-type: none"> <li>1. CPP-1X active + sulindac active vs. CPP-1X placebo + sulindac active, and</li> <li>2. CPP-1X active + sulindac active vs. CPP-1X active + sulindac placebo</li> </ol> <p>7<sup>th</sup> paragraph:          2<sup>nd</sup> sentence <b>revised</b> as “That is, assuming between 52 and 55 expected total number of events have occurred by trial end in either of the two-arm comparisons, if the log-rank critical.....”          4<sup>th</sup> and 5<sup>th</sup> sentence <b>revised</b> as “The futility analysis results will be presented in a simple manner whereby the DMC will be informed that the conditions indicating futility have been met (i.e. the futility boundary has been crossed, yes or no).”</p>
<b>Table 5.2 Interim Futility Analysis Details</b>	<p>First column – Estimated Look Time Point  <b>Deleted</b> 1.5 years. <b>Added</b> “When 45 adjudicated primary endpoints have occurred, corresponding to when 50% of maximum trial information has been amassed.”</p> <p>Second column – Description: <b>Updated</b> to read as follows:          Efficacy criterion <math>Z=1.96</math> at terminal analysis.          Futility criterion of <math>Z=0.50</math> or less at interim analysis.          Total Type I error for end of study comparison = 0.0471.          NB: Assuming D = 52 events at trial end in either two-arm comparison, power = 0.8566.          Assuming D = 55 events at trial end in either two-arm comparison, power = 0.8750.</p>
<b>Added New Section 5.2.2 Adjudication Committee (AC)</b>	<p><b>Added</b> A blinded adjudication committee (AC) will be formed for the purpose of reviewing all possible primary outcomes, for all randomized patients. The committee will be composed of one or more clinical specialists with experience and expertise in treatment of FAP. The process will follow other reported AC review procedures used in clinical trials with interim analyses[3].</p> <p>To organize the review process, a subject profile document will be developed in advance of the first review cycle, which will contain all information deemed necessary for the AC review. Elements of the profile will include subject eligibility, baseline characteristics, investigator assessment of primary endpoint status, other information related to study primary endpoint status, and related investigator comments, as collected by the EDC system. On a periodic basis, upon request from the Sponsor, the CRO will prepare one profile document for each subject that has completed the treatment phase of the study. If auxiliary information is requested by the AC, documents will be made available to the AC where ever possible.</p> <p>The AC will review the profile information in a secure manner and submit a reviewer worksheet, indicating their assessment of whether or not the data indicate that the subject reached an FAP-related event. For each withdrawal from follow-up for reasons other than an FAP-related event (including those subjects that decline the extended treatment after completing 24 months of treatment), the AC will determine whether or not the reasons recorded for the withdrawal can be deemed unrelated to endpoint status. If the AC deems the reasons for withdrawal unrelated to endpoint status, the withdrawal will be entered as a censored observation as of the time of the last recorded clinic visit. If the AC cannot deem the withdrawal as unrelated to endpoint status, the withdrawal will be considered an imputed primary endpoint on grounds of treatment failure. The follow-up time will be as of the last recorded clinic visit.</p>

Section	Change or Revision
	<p>The committee will be blinded to treatment assignment without exception. All AC review results will be forwarded on to the CRO for data entry and future reporting of AC findings.</p> <p>The AC will be instructed to apply the following criterion to determine whether or not the withdrawal is “unrelated to endpoint status.” The key is to determine whether or not the censoring is plausibly non-informative about the additional time it would take to observe an FAP-related event if the subject continued in the trial. More precisely, the AC will first be asked to contemplate the statistical distribution of the additional time to wait for an actual FAP-related event for the given subject, assuming counterfactually that the subject had not withdrawn and instead continued in the trial, while <i>taking account</i> of the reasons the subject has in fact given for his or her withdrawal. This distribution need not be known explicitly, merely conceptually, as in a thought experiment. According to the reasons given, the AC may assume the subject would remain on or come off study medication in the hypothetical continuation, whichever the clinically relevant assumption might be. Then the AC will be asked to again contemplate the same statistical distribution (i.e., the additional waiting time to an actual FAP-related event assuming counterfactually that the subject had not withdrawn and instead continued in the trial), but this time <i>completely ignoring</i> the reasons given for the subject’s withdrawal (assuming the same hypothetical continuation or discontinuation of study medication as in the first instance). If these two distributions are plausibly the same, then the withdrawal is non-informative about the additional waiting time to an FAP-related event and the censoring time is statistically independent of the time to an FAP-related event. In other words, the withdrawal is “unrelated to endpoint status” and will be handled as a censored observation. If the two distributions are plausibly different, then the withdrawal is informative and the censoring time is not statistically independent of the time to an FAP-related event. In other words, the withdrawal is not “unrelated to endpoint status” and will be handled as an imputed primary endpoint on grounds of treatment failure. Examples of reasons related or unrelated to endpoint status will be given to the AC.</p> <p>These adjudication decisions are required because for a time-to-event analysis with censoring, the censoring times must be statistically independent of the times to primary endpoint. Distinguishing between independent censored observations and imputed primary endpoints on grounds of treatment failure will also enhance the clinical meaningfulness of the comparisons in the trial.</p>
<b>Section 5.3.1, Demographic and Baseline Characteristics</b>	<p>2<sup>nd</sup> paragraph: <b>Added</b> ‘and country’  <b>Deleted</b> “(Tables 9.1-9.3, Section 9 Appendices)  <b>Added</b> last sentence “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.”</p>
<b>Section 5.3.2 Patient Disposition and Treatment Summaries</b>	<p>2<sup>nd</sup> paragraph  <b>Deleted</b> “and will include pretreatment group enumeration of all patients randomized, number ineligible, early termination due to AE/SAE, the number of subjects with an SAE, deaths, dropout for other reasons, and the number of subjects,”  <b>Changed To</b> “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 for more than 90 days, withdrawals of consent for continued follow-up, withdrawals for other reasons, and the number lost to follow-up.”  <b>Changed</b> “Additional summaries will include reasons for patients discontinuing treatment and/or modifying treatment dosages and a summary of patients’ treatment status. <b>To</b> “Additional summaries will include reasons for patients discontinuing treatment and/or modifying treatment dosages.”  <b>Deleted</b> in the last paragraph, last sentence “(Tables 9.4-9.7 in Section 9, Appendices).”</p>
<b>Section 5.3.3</b>	<p>3<sup>rd</sup> paragraph  <b>Revised</b> “If an FAP related event occurs, that patient will be said to have an observed or</p>

Section	Change or Revision
	<p>uncensored event and will be considered a treatment failure. As explained above in Section 5.2.2, if the endpoint determination cannot be made at the end of study clinic visit per the pre-specified study requirements, a blinded adjudication committee will review the reasons for such deviations. If upon blinded adjudication it can be determined that a subject's withdrawal is for reasons deemed unrelated to his or her endpoint status, that subject will be treated as a censored observation as of the last patient visit. If upon blinded adjudication it cannot be determined that a subject's withdrawal is unrelated to endpoint status, an imputed primary endpoint will be used in the primary analysis for such withdrawals. The time to this imputed event will be from randomization to the last recorded patient visit. All other subjects who complete their follow-up without a FAP related event by the end of the study will be treated as a censored observation as of the actual follow-up time for the close-out visit. See Section 5.3.6 below for further details of handling missing data."</p> <p><b>Added</b> paragraph 4 as follows          "Prior to the primary analysis, balance will be assessed between the three arms in terms of key potential confounders measured at the baseline visit. A brief list of such potential confounders will be presented to the DMC for approval prior to analysis. 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 the primary analysis using a stratified Cox model including that term in addition to the treatment arm. The covariate-adjusted score test (adjusted stratified log-rank test) will serve as the primary result for the trial."</p>
<b>Section 5.3.5 Assessment of Toxicities</b>	<b>Deleted</b> "(Tables 9.8 – 9.17, in Section 9 Appendices)"
<b>Section 5.3.6 General Procedures for Handling Missing Data</b>	<p>2<sup>nd</sup> paragraph, <b>Added</b> 6<sup>th</sup> sentence "A study event adjudication committee (AC) will be formed to further define the methods for defining imputed and censored events (see Sections 4.4 and 5.2.2)."</p> <p>3<sup>rd</sup> paragraph: Changed ICH reference from "<i>September, 1998</i>" to "<i>February, 1998</i>"</p>
<b>Section 5.4 Health Related Quality of Life Statistical Methods</b>	1 <sup>st</sup> sentence <b>Added</b> "...24 , 30 and 36 months..."
<b>Section 5.5 Dietary Assessment</b>	<b>Deleted</b> last sentence "The results of the FFQ will be used to corroborate results from another recent trial 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 could lead to dietary restrictions in combination with the combined eflornithine sulindac therapy."
<b>Section 7.2, Draft Tables Listings and Figures</b>	<p><b>Added</b> Section as these have been deleted as an appendix to the SAP.</p> <p>"The TLF (Tables, Listings, Figures) templates and shells are noted as Ver. 2.0, October 6, 2014 (SAP Ver. 3.0 September 30, 2014) based on revision provided from Data Management/Statistical Group at Ockham now Chiltern. These draft templates have been removed as an Appendix to the amended SAP and are available upon request."</p>
<b>References</b>	<b>Added</b> Schoenfeld D Biometrika (1981) 68, 316-319, also cited on page 10 Section 5.1.
<b>Appendices</b>	<b>Deleted</b> Appendices, refer to Section 7.2
<b>End</b>	

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Summary of SAP Changes Ver. 4.0, 15February2016 to Ver. 4.1, 27December2016																
Section		Change or Revision														
Global Changes		Changed version to Ver. 4.1 27 December, 2016; updated TOC														
Section 1. List of Abbreviations		Deleted AC – Adjudication Committee; Added CEC Clinical Events Committee (also referred to an Adjudication Committee)														
Section 3.2 Study Objectives and Primary Hypothesis Testing		1 <sup>st</sup> paragraph, Inserted: “Sections” in front of 5.1 added: “and 5.3.3” at the end of the paragraph. Deleted: last paragraph														
Section 4.4 Other Populations		<p>Revised the first 3 paragraphs from: “Within the entire study patient population there will be subsets who did not receive the full course of per protocol treatment. The patient diary and pill count will define the extent of compliance. This subgroup of patients will be categorized into various cohorts. For consistency, an adjudication committee will be established, to review all study events (i.e. FAP related events and dropouts), and categorize them either as censored observations or imputed endpoints (see Section 5.2.2). For exploratory and sensitivity analysis the following dropout subsets will be included in secondary analyses:”</p> <p>Revised to: “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.</p> <p>Since the goal of this trial is to delay the time to FAP-related disease progression, there may be some patients with polyposis progression and/or disease related symptoms who will discontinue treatment. An independent blinded Clinical Events Committee (CEC), also referred to as an adjudication committee will be established (vide infra), to review and confirm all Investigator determined FAP-related events and to assess all other off-study subjects for symptoms or signs of possible disease related progression that may or may not be delineated in the protocol. Section 5.2.2 provides detailed information as to decision making between the censoring vs. imputed FAP-related event.</p> <p>For exploratory and sensitivity analyses the following dropout subsets will be included in secondary analyses:”</p>														
Section 5.1 Determination of Sample Size		<p>3<sup>rd</sup> paragraph revised from: “In total we expect to observe 35+35+20=90 primary endpoints among the three groups (plus or minus 5.7). To achieve this number of events, we plan to have a 3 year study (with up to 12 months enrollment assuming no sample size reassessment plus 2 years of treatment and follow-up for the last-enrolled patients).”</p> <p>Revised to: “In total we expect to observe 35+35+20=90 primary endpoints among the three groups (plus or minus 5.7). To achieve this number of events, 171 subjects have been randomized and some will receive up to 3 years of treatment.”</p> <p>End of 4<sup>th</sup> paragraph revised from: “Table 5.1 below.”</p> <p>Revised to: “table 3.2”</p> <p>Deleted: “Table 5.1 Estimated Overall Event Free Proportions after Two Years of Follow-up</p> <table><tr><th>Treatment</th><th>S(t)</th><th>t (months)</th><th>Median Time to Event (months)*</th></tr><tr><td>Combination</td><td>0.6</td><td>24</td><td>32.5660</td></tr><tr><td>Single Agent</td><td>0.3</td><td>24</td><td>13.8172</td></tr></table> <p>*Based on an assumed exponential time-to-event distribution.”</p>			Treatment	S(t)	t (months)	Median Time to Event (months)*	Combination	0.6	24	32.5660	Single Agent	0.3	24	13.8172
Treatment	S(t)	t (months)	Median Time to Event (months)*													
Combination	0.6	24	32.5660													
Single Agent	0.3	24	13.8172													
Section 5.2		Changed section title to: Data Monitoring Committee (DMC) and Clinical Events Committee (CEC)														
Section 5.2.1 Data Monitoring Committee (DMC) and Clinical Events Committee (CEC)		<p>2<sup>nd</sup> paragraph, Deleted: ...separately at a later time...</p> <p>2<sup>nd</sup> paragraph, Deleted: ...event rates. “Pre-specified interim analyses will be conducted in a blinded (A versus B) manner.”</p>														

Summary of SAP Changes Ver. 4.0, 15February2016 to Ver. 4.1, 27December2016	
Section	Change or Revision
	<p><b>5<sup>th</sup> paragraph added first sentence:</b> “A pre-specified interim futility analysis will be conducted in a blinded manner.”</p> <p><b>5<sup>th</sup> paragraph, Deleted:</b> ...total of 45 “adjudicated”...</p>
<b>Table 5.2 Interim Futility Analysis Details</b>	<p>First column – Estimated Look Time Point</p> <p><b>Deleted:</b> adjudicated</p>
<b>Added New Section 5.2.2 Adjudication Committee (AC)</b>	<p><b>Changed section title to:</b> Clinical Events Committee (CEC)</p> <p><b>First 4 paragraphs revised from:</b> “A blinded adjudication committee (AC) will be formed for the purpose of reviewing all possible primary outcomes, for all randomized patients. The committee will be composed of one or more clinical specialists with experience and expertise in treatment of FAP. The process will follow other reported AC review procedures used in clinical trials with interim analyses[4].</p> <p>To organize the review process, a subject profile document will be developed in advance of the first review cycle, which will contain all information deemed necessary for the AC review. Elements of the profile will include subject eligibility, baseline characteristics, investigator assessment of primary endpoint status, other information related to study primary endpoint status, and related investigator comments, as collected by the EDC system. On a periodic basis, upon request from the Sponsor, the CRO will prepare one profile document for each subject that has completed the treatment phase of the study. If auxiliary information is requested by the AC, documents will be made available to the AC where ever possible.</p> <p>The AC will review the profile information in a secure manner and submit a reviewer worksheet, indicating their assessment of whether or not the data indicate that the subject reached an FAP-related event. For each withdrawal from follow-up for reasons other than an FAP-related event (including those subjects that decline the extended treatment after completing 24 months of treatment), the AC will determine whether or not the reasons recorded for the withdrawal can be deemed unrelated to endpoint status. If the AC deems the reasons for withdrawal unrelated to endpoint status, the withdrawal will be entered as a censored observation as of the time of the last recorded clinic visit. If the AC cannot deem the withdrawal as unrelated to endpoint status, the withdrawal will be considered an imputed primary endpoint on grounds of treatment failure. The follow-up time will be as of the last recorded clinic visit.</p> <p>The committee will be blinded to treatment assignment without exception. All AC review results will be forwarded on to the CRO for data entry and future reporting of AC findings.”</p> <p><b>Revised to:</b> “An independent, blinded CEC will be formed for the purpose of reviewing, confirming or adjudicating primary FAP-disease related endpoint status for all randomized patients. The committee will be composed of clinical specialists with experience and expertise in treatment of FAP. The process will follow other reported CEC review procedures. [4].</p> <p>To organize the review process, a subject profile document will be developed which will contain all information deemed necessary for the CEC review. Elements of the profile will include subject eligibility, baseline characteristics, investigator assessment of primary endpoint status, other information related to study primary endpoint status, and related investigator comments, as collected by the EDC system. On a periodic basis, the CRO will prepare one profile document for each subject that has a reported FAP-related event, completed the treatment phase, or has come off study for other reasons (e.g., withdrew consent, lost to follow-up, adverse event). If auxiliary information is requested by the CEC, documents will be made available to the CEC where ever possible.</p> <p>The CEC will review the profile information in a secure manner and submit a reviewer worksheet, with their assessment of whether the data indicate that the subject reached an FAP-related event. For each withdrawal from follow-up for reasons other than an FAP-related event (including those subjects that decline the extended treatment after completing 24 months of treatment), the CEC will determine whether the reasons recorded for the withdrawal can be deemed related to FAP disease progression not otherwise defined in the protocol or unrelated to endpoint status. If the CEC deems the reasons for withdrawal</p>

Summary of SAP Changes Ver. 4.0, 15February2016 to Ver. 4.1, 27December2016	
Section	Change or Revision
	<p>unrelated to endpoint status, the withdrawal will be entered as a censored observation as of the time of the last recorded clinic visit.</p> <p>If the CEC assesses and adjudicates the patient status at the completion of treatment or at the time off-study for clinical symptoms or signs likely related to FAP disease progression an imputed primary endpoint as of the last recorded clinic visit will be entered.</p> <p>The committee will be blinded to treatment assignment without exception.”</p> <p><b>Deleted:</b> Last 2 paragraphs</p>
<b>Section 5.3.3, Analytic Methods for Time-to Event Data</b>	<p><b>3<sup>rd</sup> paragraph Deleted:</b> “As explained above in Section 5.2.2, if the endpoint determination cannot be made at the end of study clinic visit per the pre-specified study requirements, a blinded adjudication committee will review the reasons for such deviations.”</p> <p><b>4<sup>th</sup> paragraph changed: from:</b> “last patient visit <b>to:</b> last recorded clinic visit”</p> <p><b>5<sup>th</sup> paragraph deleted and changed to:</b> “If upon blinded adjudication the CEC considers the early withdrawal to be consistent with disease progression (not specifically an FAP-related event as defined in the FAP-310 protocol), the patient will be determined to have an imputed FAP-related event. The time to this imputed event will be from randomization to the last recorded clinic visit.”</p>
<b>Section 5.3.6 General Procedures for Handling Missing Data</b>	<p><b>2<sup>nd</sup> paragraph, Added fist sentence 1<sup>st</sup> paragraph:</b> “an imputed FAP-related event”;</p> <p><b>2<sup>nd</sup> paragraph Deleted:</b> “A patient will be considered a treatment failure if for any reason, the endpoint determination cannot be made per the pre-specified protocol. The time to this imputed event will be from randomization to the last recorded patient visit. A study event adjudication committee (AC) will be formed to further define the methods for defining imputed and censored events (see Sections 4.4 and 5.2.2). Any secondary or sensitivity analysis that includes this assumption will be clearly noted. Similarly, any sensitivity analysis that incorporates the last observation carried forward (LOCF) method, to compensate for early patient dropouts or missing data, will be clearly noted.”</p> <p><b>3<sup>rd</sup> paragraph Revised from:</b> “Secondary analysis data include the presence of a specific genetic mutation, and urinary metabolite concentrations (see Section 3.2.2). The primary analysis of the secondary objectives will include collected data only, without imputing or weighting data to compensate for missing data. 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)”.”</p> <p><b>Changed to:</b> “Secondary analysis data include the presence of a specific genetic mutation, and urinary metabolite concentrations (see Section 3.2.2). 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)”.”</p>
<b>Section 5.5 Dietary Assessment</b>	<b>1<sup>st</sup> paragraph last sentence, Inserted</b> “are” after questionnaire
<b>End</b>	

**Study ID: CPP FAP-310, 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)**

**Summary of SAP Changes Ver. 4.1, December 27, 2016 to Ver. 4.2 May 15, 2017**

Section	Change or Revision
<b>Global Changes</b>	<b>Changed</b> version to Ver. 4.2, May 15, 2017
<b>TOC</b>	<b>Updated:</b> Table of Contents, and list of tables and figures
<b>Sec. 1 List of Abbreviations</b>	<b>Added:</b> Z-score, The value of the critical ratio (score statistic divided by its standard error) based on the stratified log-rank statistic.
<b>Section 3.2 Study Objectives and Primary Hypothesis Testing</b>	<p><b>Revised from:</b></p> <ol style="list-style-type: none"> <li>1. CPP-1X active + sulindac active vs. CPP-1X placebo + sulindac active, and</li> <li>2. CPP-1X active + sulindac active vs. CPP-1X active + sulindac placebo</li> </ol> <p>Each comparison will be performed at the 2-sided <math>p = 0.05</math> level.</p> <p><b>Revised to:</b></p> <ol style="list-style-type: none"> <li>3. CPP-1X placebo + sulindac active vs. CPP-1X active + sulindac active, and</li> <li>4. CPP-1X active + sulindac placebo vs. CPP-1X active + sulindac active</li> </ol> <p>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 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.</p> <p>Each comparison will be performed at the 2-sided 0.05 level of statistical significance.</p>
<b>Sect. 3.2.1 Regulatory Review of Primary Outcome Compliance</b>	<p><b>Revised from:</b></p> <p>The US Food and Drug Administration (FDA) noted that the comparison of CPP-1X + sulindac vs. CPP-1X + placebo will not provide information about the treatment effect of CPP-1X (i.e. eflornithine), and therefore this result will not be included in the product label. Therefore, the primary analysis of import to FDA is the comparison of CPP-1X + sulindac vs. sulindac + placebo.</p> <p><b>Revised to:</b></p> <p>The US Food and Drug Administration (FDA) noted that the comparison of single agent CPP-1X vs. combination treatment will not provide information about the treatment effect of CPP-1X (i.e. eflornithine), and therefore this result will not be included in the product label. Therefore, the primary analysis of import to FDA is the comparison of single agent sulindac vs. combination treatment.</p>
<b>Sect.5.1 Determination of Sample Size</b>	<p><b>Revised from:</b></p> <ol style="list-style-type: none"> <li>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, for each of the two between-group comparisons (i.e. CPP-1X plus sulindac vs. CPP-1X and CPP-1X plus sulindac vs. sulindac);</li> </ol> <p><b>Revised to:</b></p> <ol style="list-style-type: none"> <li>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 discrete time (visit month number), 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);</li> </ol>

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**Summary of SAP Changes Ver. 4.1, December 27, 2016 to Ver. 4.2 May 15, 2017**

Section	Change or Revision
	<p><b>Revised from:</b></p> <p>3) Power of at least 85% to detect the above-mentioned treatment effect comparing the combination arm vs. either of the two single treatment arms;</p> <p><b>Revised to:</b></p> <p>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;</p> <p><b>Added paragraph after 4):</b>          The following calculations are based on our review of limited single-agent data for eflornithine and sulindac, in which the 2-year event free rates imply a single overall event free rate of 60% for combination treatment group and 30% in each single agent treatment group. This is described further in Table 3.2.</p> <p><b>Revised from:</b>          Even if the total number of events in either comparison were only 43, there will still be 80% power to detect the design effect size, namely, a hazard rate ratio of <math>0.4243 = (\ln 0.60)/(\ln 0.30)</math> corresponding to the doubling of event-free follow-up over two years.</p> <p>In total we expect to observe <math>35+35+20=90</math> primary endpoints among the three groups (plus or minus 5.7). To achieve this number of events, 171 subjects have been randomized and some will receive up to 3 years of treatment.</p> <p>This is based on our review of limited single-agent data for eflornithine and sulindac, in which the 2-year event free rates imply a single overall event free rate of 60% for combination treatment group and 30% in each single agent treatment group. This is described further in Table 3.2.</p> <p><b>Revised to:</b>          Even if the total number of events in either comparison were only 43, there will still be 80% power to detect the design effect size, namely, a hazard rate ratio of <math>(\log 0.30)/(\log 0.60)</math> corresponding to the doubling of event-free follow-up over two years (approximately equal to 2.3569). For completeness, the design effect size is equivalent to a hazard rate ratio of <math>(\log 0.60)/(\log 0.30)</math> for the combination treatment relative to a single-agent treatment (approximately equal to 0.42428).</p> <p>In total we expect to observe <math>35+35+20=90</math> primary endpoints among the three groups (plus or minus 5.7).</p>
<b>Sect. 5.2.1</b> <b>Data</b> <b>Monitoring</b> <b>Committee</b> <b>(DMC)</b>	<p><b>Paragraph 3,</b></p> <p><b>Revised from:</b>          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.</p> <p><b>Revised to:</b>          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 efficacy and futility.</p>

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Section	Change or Revision
	<p><b>Paragraph 5</b>  <b>Revised from:</b> A pre-specified interim futility analysis will be conducted in a blinded manner. The futility 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.  <b>Revised to:</b> A pre-specified interim efficacy and futility analysis will be conducted as described below. 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. After reviewing the analysis results in a closed session, the DMC will provide recommendations regarding possible termination of the study for either futility, efficacy, or safety reasons, to the Sponsor Steering Committee</p> <p><b>Paragraph 6</b>  <b>Revised from:</b>          The futility analysis will be performed for each of the two treatment comparisons contained in the primary objective:</p> <ol style="list-style-type: none"> <li>1. CPP-1X active + sulindac active vs. CPP-1X placebo + sulindac active,</li> <li style="text-align: center;">and</li> <li>2. CPP-1X active + sulindac active vs. CPP-1X active + sulindac placebo</li> </ol> <p>For the futility interim analysis, the futility stopping criterion of <math>Z=0.50</math> is one-sided, and corresponds to a conditional power criterion of approximately 0.12 (to two decimals). That is, assuming between 52 and 55 expected total number of events have occurred by trial end in either of the two-arm comparisons, 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, then under the design alternative hazard ratio of 0.4243, there would be only a 12% probability (or less) 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 the trial for futility. The futility analysis results will be presented in a simple manner whereby the DMC will be informed that the conditions indicating futility have been met (i.e. the futility boundary has been crossed, yes or no). The details of the futility analysis are provided in <b>Error! Reference source not found.</b> below. Unless the DMC requires it on ethical grounds, no early stopping for positive efficacy is proposed.</p> <p><b>Revised to:</b>          The analysis will be performed for each of the two treatment comparisons contained in the primary objective:</p> <ol style="list-style-type: none"> <li>1. CPP-1X placebo + sulindac active vs. CPP-1X active + sulindac active,</li> <li style="text-align: center;">and</li> <li>2. CPP-1X active + sulindac placebo vs. CPP-1X active + sulindac active.</li> </ol> <p>As stated above in Section 3.2, the combination of CPP-1X active + sulindac active is specified as the reference treatment group because it is common to both comparisons and 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.</p>

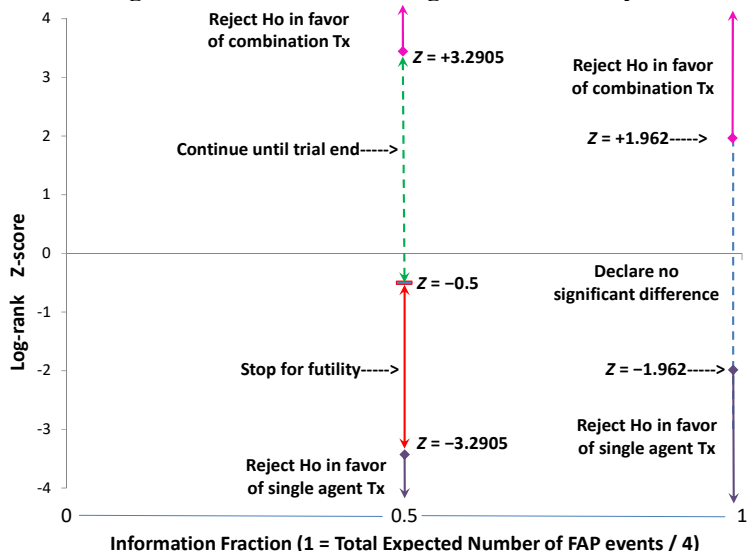
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	<p>The efficacy analysis will use a modified Haybittle-Peto stopping rule based on the stratified log-rank Z-score. If that Z-score equals or exceeds 3.2905 in absolute value, for either two-arm comparison, the difference between treatment arms would 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.</p> <p>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 <math>Z = -0.50</math>. That is, if the Z-score is less than or equal to <math>-0.50</math>, 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 <math>Z = -0.50</math> 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 <math>-0.5</math> (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.</p> <p>The details of the efficacy and futility analysis are provided in <b>Error! Reference source not found.</b> below. Figure 5.1 presents a schematic diagram of the procedure, and Table 5.2 provides more precise conditional power values corresponding to the futility criterion <math>Z = -0.50</math> as a function of the total number of events in either two-arm comparison. See Section 7.4 below for further details of the conditional power calculation.</p>
<b>Table 5.1</b> <b>Interim</b> <b>Futility</b> <b>Analysis</b> <b>Details</b>  <b>Description</b>	<p><b>Revised From:</b></p> <p>Efficacy criterion <math>Z=1.96</math> at terminal analysis.</p> <p>Futility criterion of <math>Z=0.50</math> or less at interim analysis.</p> <p>Total Type I error for end of study comparison = 0.0471.</p> <p>NB: Assuming D = 52 events at trial end in either two-arm comparison, power = 0.8566. Assuming D = 55 events at trial end in either two-arm comparison, power = 0.8750.</p> <p><b>Revised To:</b></p> <p>Efficacy criterion <math>Z = 1.962</math> at terminal analysis.</p> <p>Futility criterion of <math>Z = -0.50</math> or less at interim analysis.</p> <p>Type I error for exiting the upper efficacy boundary at or before terminal analysis = 0.024952.*</p> <p>Type I error for exiting the lower efficacy boundary at or before terminal analysis = 0.001984.*</p> <p>Total Type I error for end of study comparison = 0.026936.*</p> <p>Assuming 52 events at trial end in either two-arm comparison, power = 0.8705.</p> <p>Assuming 55 events at trial end in either two-arm comparison, power = 0.8881.</p> <p>*Assume one interim analysis at <math>\frac{1}{2}</math> information time with upper efficacy boundary at <math>B_e = 3.2905</math>, lower efficacy boundary at <math>-B_e</math>, and one-sided futility boundary</p>

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Section	Change or Revision																					
	<p><math>B_f = -0.50</math>. Assume upper efficacy terminal criterion <math>C = 1.9602</math> and lower efficacy terminal criterion <math>-C</math>. Then the probability of exiting the upper efficacy boundary at either interim or terminal analysis under the null hypothesis is given by</p> $\Phi(-B_e) + \int_{B_f}^{B_e} \Phi(z - C\sqrt{2})\varphi(z)dz$ <p>and the probability of exiting the lower efficacy boundary at either interim or terminal analysis under the null hypothesis is given by</p> $\Phi(-B_e) + \int_{B_f}^{B_e} \Phi(-z - C\sqrt{2})\varphi(z)dz ,$ <p>where <math>\varphi(z)</math> is the standard normal probability density function and <math>\Phi(z)</math> is the standard normal cumulative distribution function.</p>																					
Sect. 5.2.1	<p><b>Added: Figure 5.1: Schematic Diagram for Futility and Terminal Analyses</b></p> 																					
Sect. 5.2.1	<p><b>Added: Table 5.2 Conditional Power at the Futility Boundary as a Function of Number of FAP Events at the Time of Futility Analysis, Using Futility Criterion <math>Z = -0.5</math></b></p> <table><tr><th>Total FAP events in either two-arm comparison at time of futility analysis</th><th>Assumed number of FAP-related events in either two-arm comparison at trial conclusion</th><th>Conditional power</th></tr><tr><td>30</td><td>60</td><td>0.177</td></tr><tr><td>29</td><td>58</td><td>0.167</td></tr><tr><td>28</td><td>56</td><td>0.157</td></tr><tr><td>27</td><td>54</td><td>0.148</td></tr><tr><td>26</td><td>52</td><td>0.138</td></tr><tr><td>25</td><td>50</td><td>0.129</td></tr></table>	Total FAP events in either two-arm comparison at time of futility analysis	Assumed number of FAP-related events in either two-arm comparison at trial conclusion	Conditional power	30	60	0.177	29	58	0.167	28	56	0.157	27	54	0.148	26	52	0.138	25	50	0.129
Total FAP events in either two-arm comparison at time of futility analysis	Assumed number of FAP-related events in either two-arm comparison at trial conclusion	Conditional power																				
30	60	0.177																				
29	58	0.167																				
28	56	0.157																				
27	54	0.148																				
26	52	0.138																				
25	50	0.129																				

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**Summary of SAP Changes Ver. 4.1, December 27, 2016 to Ver. 4.2 May 15, 2017**

Summary of CHM Changes: Ver. 1.1; December 27, 2016 to Ver. 1.2; May 18, 2017					
Section	Change or Revision				
		24	48	0.120	
		23	46	0.111	
		22	44	0.103	
Sect. 5.2.2 CEC	3 <sup>rd</sup> paragraph 4 <sup>th</sup> sentence, deleted the following text: “(including those subjects that decline the extended treatment after completing 24 months of treatment)”				
Sect. 5.3.3 Analytic Methods for Time to Event Data	1 <sup>st</sup> paragraph Revised from: The analytic method for the primary analysis will be a time-to-event analysis using the stratified log-rank test, as previously described. Stratified Cox proportional hazards regression models will be used for secondary assessments[7]. Graphical analyses (log-minus-log plots) will be used to check the assumption of constant hazard ratios.  Revised to: The analytic method for the primary analysis will be a time-to-event analysis using the stratified log-rank test, as previously described. The discrete time version of the log-rank statistic using visit month number 0, 6, 12, 18, 24, 30, 36 will be used. Stratified discrete-time Cox proportional hazards regression models will be used for secondary assessments[7]. Graphical analyses (log-minus-log plots) will be used to check the assumption of constant hazard ratios. See Section 7.3 below for further details of the calculation of the discrete time stratified log-rank statistic.				
New Sect. 7.3	Added Section: 7.3 Details of Calculating the Discrete-time Stratified Log-rank Z-Score Patient follow-up will be analyzed in discrete time, with events occurring at the 6, 12, 18, 24, 30, 36 month visits and censorings also possible at the baseline visit at month 0 for patients who dropped out of the trial before their first follow-up visit. Therefore, the primary test statistic will be the discrete-time stratified log-rank statistic, which is equivalent to the score-test statistic from Cox’s original discrete-time partial likelihood function. Each two-arm comparison will be performed separately This will be implemented in SAS by specifying the TIES=DISCRETE option in PROC PHREG. The single agent treatments will be coded as 1 and the combination treatment will be coded as 0. The square root of the score test chi-squared statistic will be calculated and the <i>sign</i> of the estimated log hazard ratio (+ if the HR>1 and – if the HR<1) will be attached. This results in discrete-time stratified log-rank Z-score. In symbols, $Z_k = sign(\hat{\beta}) \times \sqrt{X^2}$ , where $\hat{\beta}$ denotes the estimated log hazard ratio coefficient for treatment A in the Cox model and where $X^2$ denotes the SCORE TEST chi-squared statistic reported within the “Testing Global Null Hypothesis: BETA=0” table at the top of the PHREG results section. The following sample PHREG procedure could be used in SAS to derive the stratified log-rank Z-score: <pre>proc phreg data=TwoArmData; model time*censor(1) = Treatment / rl ties=discrete; strata Stratification_Factor; title "Stratified Cox Regression Analysis for Single Agent vs Combination"; run; quit;</pre>				

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Section	Change or Revision
New Sect. 7.4	<p><b>Added Section:</b>  <b>7.4 Details of Calculating Conditional Power</b>            Conditional power is given by the following formula[20].</p> $\text{Conditional power} = \Phi \left( \frac{Z_k \sqrt{I_k} - z_{1-\alpha/2} \sqrt{I_K} + \theta(I_K - I_k)}{\sqrt{I_K - I_k}} \right),$ <p>where</p> <p><math>Z_k</math> is the value of the stratified log-rank test statistic from the observed data at interim analysis;  <math>z_{1-\alpha/2}</math> is the critical value for a two-tailed test at <math>\alpha=0.05</math>, namely +1.962 adjusted for the interim efficacy analysis;  <math>I_K</math> = the information number expected at trial end = <math>\frac{1}{4}</math> times the total expected number of events;  <math>I_k</math> = the information number at futility analysis = <math>\frac{1}{4}</math> times the observed number of events at interim analysis;  <math>\theta</math> is the log hazard ratio at the design alternative, <math>\log 2.3569 = -\log 0.42428 = +0.85736</math>; and <math>\Phi(\cdot)</math> is the standard normal cumulative distribution function.</p> <p><u>Example.</u> Suppose at the time of interim analysis, the number of FAP-related events are as follows: For single-agent treatment A, 20; for single-agent treatment B, 16; and for combination treatment C, 9. Then in the two-arm comparison of A versus C, there would be a total of 29 events, so the information number is <math>I_k=29/4=7.25</math>. We assume that there will be double this number for the corresponding comparison at the end of the trial; thus <math>I_K = 14.5</math>. Suppose the Z-score at the futility analysis happens to just equal the futility criterion, i.e., suppose <math>Z_k = -0.50</math>. Then applying the above formula yields conditional power of</p> $\Phi \left( \frac{-0.5\sqrt{7.25} - 1.962\sqrt{14.5} + 0.85736(14.5 - 7.25)}{\sqrt{14.5 - 7.25}} \right) = 0.1670.$ <p>This is the conditional power <i>at the futility boundary</i>. Suppose, however, that the observed Z-score at the futility analysis were actually +0.50 instead of -0.5. Then the -0.5 in the first term of the above expression would be replaced by <math>Z_k=+0.50</math>, and the resulting <i>observed</i> conditional power would be 0.5135, a non-futile result.</p> <p>Note that the probability of a significant <i>negative</i> result at the terminal analysis, given that there is no stopping for futility at the interim analysis, is not included in the above expression. That is because practical interest for futility analysis resides only in the conditional probability of a significant benefit of the combination treatment. In any case, the term which has been omitted is numerically negligible.</p>
Sect. 8 References	<p><b>Added Ref 20</b>            Jennison, C. and B. W. Turnbull (2000). Group sequential methods with applications to clinical trials. Boca Raton, Chapman &amp; Hall/CRC.</p>
End	

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**Summary of SAP Changes Ver. 4.2 May 15, 2017 to Ver. 4.3 July21, 2017**

Section	Change or Revision
<b>Global</b>	<b>Changed</b> version to Ver. 4.3, July21, 2017
<b>Sec 2.</b>	2 <sup>nd</sup> paragraph <b>revised</b> sentence as follows: “...delaying the time from the date of randomization to the date of the first occurrence of any FAP-related event....”
<b>Sec. 3.1</b>	2 <sup>nd</sup> paragraph <b>revised</b> with treatment extension assessment points. Eligible patients who have given informed consent will enter the study with the intent to participate for the full treatment period of 24 months. Based on a subject’s date of randomization, patients will be offered continued preparticipation in blinded treatment for up to a total of 36, 42 or 48 months of treatment if they have completed the initial 24 months of treatment without an FAP event <del>may continue treatment for up to 12 additional months</del> until one of the following occurs: 1) subject has an FAP event or comes off study for other reasons, 2) all randomized subjects have reached a minimum of 24, 36, 42 or 48 months of treatment,
<b>Sec. 3.2</b>	2 <sup>nd</sup> paragraph <b>added:</b> “from the date of randomization to the date” 4 <sup>th</sup> paragraph <b>added:</b> ...is to delay the time “from randomization” to FAP-related disease progression....
<b>Sec. 4.1</b>	<b>Revised</b> definition of ITT population to: “The intent-to-treat population includes all patients that have been randomized to one of the three study arms.”
<b>Sec. 4.4</b>	4 <sup>th</sup> paragraph <b>revised</b> CEC review and process:  Section 5.2.2 provides detailed information on the CEC process and how the results will be used for sensitivity analyses and quality assurance purposes.  For exploratory and sensitivity analyses the following subsets will be included in secondary analyses:  <ul style="list-style-type: none"> <li>• CEC reviewed and adjudicated subject outcomes</li> </ul>
<b>Sec. 5.2.2</b>	1 <sup>st</sup> paragraph <b>deleted:</b> “primary FAP-disease related” 4 <sup>th</sup> paragraph <b>revised:</b>  If upon blinded adjudication the CEC considers the early withdrawal to be consistent with disease progression (not specifically an FAP-related event as defined in the FAP-310 protocol), the patient will be determined to have an imputed FAP-related event. The time to this imputed event will be from randomization to the last recorded clinic visit.  If upon blinded adjudication it can be determined that a subject’s withdrawal is for reasons deemed unrelated to his or her endpoint status, that subject will be treated as a censored observation as of the last recorded clinic visit. <del>If the CEC deems the reasons for withdrawal unrelated to endpoint status, the withdrawal will be entered as a censored observation as of the time of the last recorded clinic visit.</del>  <del>If the CEC assesses and adjudicates the patient status at the completion of treatment or at the time off study for clinical symptoms or signs likely related to FAP disease progression an imputed primary endpoint as of the last recorded clinic visit will be entered.</del>  The committee will be blinded to treatment assignment without exception.  <b>Added</b> last sentence: CEC determined imputed FAP-related events will be used for sensitivity analyses and will not be used for the primary endpoint assessment of clinical benefit.
<b>Sec. 5.3.2</b>	2 <sup>nd</sup> paragraph , 3 <sup>rd</sup> sentence <b>revised:</b>

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**Summary of SAP Changes Ver. 4.2 May 15, 2017 to Ver. 4.3 July 21, 2017**

Section	Change or Revision
	These will be further described in subgroups such as drop outs due to adverse events, serious adverse events, administrative withdrawals for non-compliance for more than 90 days from randomization to month 36 or more than 105 days from randomization to month 42 or more than 120 days from randomization to month 48, withdrawals of consent for continued follow-up, withdrawals for other reasons, and the number lost to follow-up.
5.3.3	<p>1<sup>st</sup> paragraph <b>added</b>: “, 42 and 48”</p> <p>Paragraphs 3 – 6 <b>revised</b> as follows:</p> <p>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).</p> <p>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.</p> <p>If a subject has two or more missing assessments, time to first FAP-related event for the subject will be censored at the time of last adequate evaluation prior to the missing assessment.</p> <p>If a subject has no baseline assessment, time to first FAP-related event for the subject will be censored at the date of randomization.</p> <p><del>If upon blinded adjudication it can be determined that a subject’s withdrawal is for reasons deemed unrelated to his or her endpoint status, that subject will be treated as a censored observation as of the last recorded clinic visit.</del></p> <p><del>If upon blinded adjudication the CEC considers the early withdrawal to be consistent with disease progression (not specifically an FAP-related event as defined in the FAP 310 protocol), the patient will be determined to have an imputed FAP-related event. The time to this imputed event will be from randomization to the last recorded clinic visit.</del></p> <p>8<sup>th</sup> paragraph <b>deleted</b>: A brief list of such potential confounders will be presented to the DMC for approval prior to analysis.</p>
5.3.6	2 <sup>nd</sup> paragraph <b>deleted</b> : “an imputed FAP-related event”, and next sentence deleted “for reasons deemed unrelated to their health status”....
5.4	<p><b>Added</b>: “36, 42 and 48” months</p> <p>Last paragraph <b>deleted</b>: “This trial has three strata and three treatment options with 150 patients to be entered.”</p>
5.5	<b>Added</b> : Dietary assessments via the FFQ will be obtained at baseline, “months 12, 24, 36, 42 (only if end of treatment), and 48...”
7.3	<b>Added</b> : ...”42 and 48” month visits
End	

**Study ID: CPP FAP-310, 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)**

**Summary of SAP Changes Ver. 4.3 July 21, 2017 to Ver. 5.0, April 02, 2018**

Section	Change or Revision
<b>Global</b>	<b>Changed</b> version to Ver. 5.0, April 02, 2018
<b>Sec. 3.1</b>	6 <sup>th</sup> paragraph, <b>Changed</b> , “A total of 150 eligible subjects will be enrolled, 50 per treatment group.” <b>To</b> “At least 150 eligible subjects will be enrolled, with at least 50 per treatment group.”
<b>Sec. 4.4</b>	<p>Deleted the following text</p> <p><del>Since the goal of this trial is to delay the time to FAP-related disease progression, there may be some patients with polyposis progression and/or disease-related symptoms with will discontinue treatment. An independent blinded Clinical Events Committee (CEC), also referred to as an adjudication committee will be established (vide infra), to review and confirm all Investigator determined FAP-related events and to assess all other off-study subjects for symptoms or signs of possible disease-related progression that may or may not be delineated in the protocol.</del></p> <p><del>Section 5.2.2 provides detailed information on the CEC process and the results will be used for sensitivity analyses and quality assurance purposes.</del></p> <ul style="list-style-type: none"> <li><del>CEC reviewed and adjudicated subject outcomes</del></li> </ul>
<b>Sec. 5.1</b>	<p><b>Deleted and Revised (see below):</b></p> <p>For the purposes of power calculations, we assume the following:</p> <ol style="list-style-type: none"> <li>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 discrete time (visit month number), 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);</li> <li>2) A doubling of the time to occurrence of the primary event from either of the single agent treatment arms to the combination treatment group;</li> <li>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;</li> <li>4) The two single-agent treatment groups have the same event rate.</li> </ol> <p>The following calculations are based on our review of limited single-agent data for eflornithine and sulindac, in which the 2-year event free rates imply a single overall event free rate of 60% for combination treatment group and 30% in each single agent treatment group. This is described further in <b>Error! Reference source not found.</b></p> <p>For this situation, 49 events would be needed for each two-group comparison at the 2-sided 0.05 level with 85% power and the doubling of the time to primary event[2, 3]. Assuming two-year event proportions of 70% in either of the two single-agent groups and 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 20 in the combination arm. Thus we expect to have 55 patients with a FAP-related event in each comparison, achieving almost 89% power. The standard deviation around this expectation is 4.74, so we would be highly likely to observe at least the required 49 events. Even if the total number of events in either comparison were only 43, there will still be 80% power to detect the design effect size, namely, a hazard rate ratio of <math>(\log 0.30)/(\log 0.60)</math> corresponding to the doubling of event-free follow-up over two years (approximately equal to 2.3569). For completeness, the design effect size is equivalent to a hazard rate ratio of <math>(\log 0.60)/(\log 0.30)</math> for the combination treatment relative to a single-agent treatment (approximately equal to 0.42428).</p> <p>In total we expect to observe <math>35+35+20=90</math> primary endpoints among the three groups (plus or minus 5.7).</p>

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**Summary of SAP Changes Ver. 4.3 July 21, 2017 to Ver. 5.0, April 02, 2018**

Section	Change or Revision
	<p><b>Revised with:</b></p> <p>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 protocol for tabulated listing).</p> <p>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.</p> <p>For the purposes of power calculations, we assume the following:</p> <ol style="list-style-type: none"> <li>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 (see section 7.3 for details);</li> <li>2) A doubling of the two-year event-free proportion from either of the single agent treatment arms to the combination treatment group;</li> <li>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;</li> <li>4) The two single-agent treatment groups have approximately the same event rate.</li> </ol> <p>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. This is described further in Table 3.2.</p> <p>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. Note that the primary analysis described below, in Section 7.3, does not rely on such an assumption and provides a statistically valid test of the null hypothesis even if hazard rates are not constant. Furthermore, the stratified log-rank test is an optimal test (locally most powerful) under the assumption that the <i>ratio</i> 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 <i>design alternative parameter</i> for the trial.</p> <p>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</p>

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**Summary of SAP Changes Ver. 4.3 July 21, 2017 to Ver. 5.0, April 02, 2018**

Section	Change or Revision
	<p>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 <math>\{\log(0.60) / \log(0.30)\} = 0.4243</math>. <i>This is the design alternative hazard ratio for this trial</i> 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 <i>at least</i> 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 = <math>\{\log(0.70) / \log(0.30)\}</math> (see discussion below). 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 <math>\{\log(0.30) / \log(0.60)\} = 1/0.4243 = 2.357</math>.</p> <p>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[2,3] 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.</p> <p>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.</p>
<b>Sec. 5.2.2</b>	<b>Deleted</b> section on CEC
<b>Sec. 5.3.3</b>	<p><b>Deleted:</b> The discrete time version of the log-rank statistic using visit month number 0, 6, 12, 18, 24, 30, 36, 42, and 48 will be used.</p> <p><b>Revised</b> sentence as follows:        The <del>S</del>stratified <del>discrete time</del> Cox proportional hazards regression models.....</p> <p><b>Revised</b> sentence as follows:        See Section 7.3 below for further details of the calculation of the <del>discrete time</del> stratified long-rank statistic.</p> <p>See Section 5.3.6 below for further details of handling missing data. <b>Added sentence:</b> Every effort will be made to minimize the occurrence of censoring and missing data.</p> <p><b>Deleted</b> at the end of the section “Every effort will be made to minimize the use of censoring.”</p>

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**Summary of SAP Changes Ver. 4.3 July 21, 2017 to Ver. 5.0, April 02, 2018**

Section	Change or Revision
	<p>Last paragraph:</p> <p><b>Revised:</b> 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 the primary analysis using a stratified Cox model including that term in addition to the treatment arm. The covariate-adjusted score test (adjusted stratified log-rank test) will serve as the primary result for the trial.</p> <p><b>To:</b> 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 aid in the interpretation of the primary result.</p>
<b>Sec. 6</b>	<b>Changed:</b> “A total of 150 eligible patients will be randomized in this study <b>To</b> “At least 150 eligible patients will be randomized in this study.”
<b>Sec. 7.3</b>	<p><b>Revised:</b></p> <p>Patient follow-up will be analyzed in discrete time, with events occurring at the 6, 12, 18, 24, 30, 36, 42 and 48 month visits and censorings also possible at the baseline visit at month 0 for patients who dropped out of the trial before their first follow-up visit. Therefore, the primary test statistic will be the discrete-time stratified log-rank statistic, which is equivalent to the score-test statistic from Cox’s original discrete-time partial likelihood function.</p> <p><b>To:</b></p> <p>Patient follow-up will be analyzed in continuous time, although it is recognized that FAP event detection will cluster around scheduled study visits, at months 6, 12, 18, 24, 30, 36, 42 and 48 and event times may be tied as follow-up time is measured only to the nearest day. Censorings are possible at the baseline visit (month 0) for patients who dropped out of the trial before their first follow-up visit. The primary test statistic will be the stratified log-rank statistic.</p> <p><b>Revised:</b></p> <p>This results in the <del>discrete time</del> stratified log-rank Z-score.</p> <p><b>Added:</b> “NB: The model includes the variables time, censor, and treatment, only.</p>
<b>End</b>	

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**Summary of SAP Changes Ver. 5.0, April 2, 2018 to Ver. 5.1, July 30, 2018**

Section	Change or Revision
<b>Global</b>	<ul style="list-style-type: none"> <li>• <b>Changed</b> version 5.0 April 2, 2018 to Ver. 5.1, July 30, 2018</li> <li>• Standardized the term P-value for uniformity</li> <li>• <b>Fixed:</b> Formatting and corrected typographical errors</li> <li>• <b>Updated:</b> Table of Contents, reference numbers, table numbers, and section numbers.</li> </ul>
<b>Sec. 1</b>	<p><b>Deleted:</b> CEC abbreviation and term, from list of abbreviations.</p> <p><b>Added:</b></p> <p>LGI, Lower Gastrointestinal</p> <p>LGIOI, LGI Observed Improvement</p> <p>UGI, Upper Gastrointestinal</p> <p>UGIOI, UGI Observed Improvement</p>
<b>Sec. 3.2</b>	<p><b>Added after 3<sup>rd</sup> paragraph:</b> “These two treatment comparisons will be performed sequentially, as described below.”</p>
<b>Sec. 3.2.1</b>	<p><b>Added to 4<sup>th</sup> paragraph, first sentence:</b> “sequentially” perform “the” two “primary” comparisons.....</p> <p><b>Added last paragraph:</b></p> <p>“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 <i>both</i> tests must be significant for EMA approval, the type I error of the second test in the sequence is less than 0.05.”</p>
<b>Sec. 3.2.2</b>	<p><b>Deleted:</b></p> <p>To evaluate the potentially effect-modifying properties of:</p> <ol style="list-style-type: none"> <li>a. Presence or absence of an ODC polymorphism.</li> <li>b. To evaluate the excretion of 4 urinary polyamines (diacetylspermine, n1-acetylspermidine, n8-acetylspermidine, and decarboxylated SAM).</li> </ol> <p>These five secondary variables will be assessed regardless of study outcome, but their use as potential label claims will only apply if a statistically significant treatment effect is found in the primary analysis. For the secondary efficacy analysis, for each secondary variable, a corresponding term will be added to the primary analysis as well as an interaction term (product of the treatment indicator and secondary variable). The coefficient of the interaction term (only) will be tested to determine if the secondary variable alters the magnitude of the treatment effect. Corresponding to each of the two primary analyses, the Hochberg step-up method[1] will be employed to control the overall family-wise error rate with overall alpha set at the two-sided 0.05 level.</p> <p><b>Replaced section with the following text:</b></p>

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Section	Change or Revision
	<p>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. 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.</p> <p>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 <i>any positive improvement</i> at either month 6 (compared to baseline) or at month 12 (compared to baseline or month 6), under the condition that there be <i>no worsening at either timepoint</i> (compared to the preceding timepoint). Here are the specific possibilities (where “Improvement” stands for either the UGIOI or LGIOI secondary endpoint):</p> <ul style="list-style-type: none"> <li>• If the 6-month score is –2 or –1, Improvement=NO irrespective of the 12-month score.</li> <li>• If the 6-month score is 0, then Improvement=YES if and only if the 12-month score is +1 or +2. Otherwise Improvement=NO.</li> <li>• If the 6-month score is +1 or +2, then Improvement=YES if and only if the 12-month score is greater than or equal to 0. Otherwise Improvement=NO.</li> </ul> <p>Any patient who drops out of the study before the month 12 assessment will be considered Improvement=NO.</p> <p>These binary UGIOI and LGIOI secondary efficacy endpoints will be compared in a manner analogous to the primary analysis, using the same two primary 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), and conditioning on the three disease site strata (Rectum/Pouch Polyposis, Duodenal Polyposis, Pre-colectomy). The null hypothesis of no association between treatment group and Improvement endpoints will be tested using the exact Mantel-Haenszel procedure for combining the evidence contained in the fourfold tables (Treatment=Single agent vs. Combination cross-classified by Improvement=YES vs. NO) across the three strata. For each of the two treatment comparisons, exact Mantel-Haenszel <i>P</i>-values will be calculated for both the UGI and LGI assessments (using the point-probability method based on the convolution of three independent central hypergeometric distributions; see [1]).</p> <p>The overall type I error for the secondary efficacy analysis will be controlled using the Hochberg step-up method for multiple comparisons[2]. This analysis will be performed in the ITT population. The primary analysis will serve as a gatekeeper to control the overall type I error rate at 0.05 for both primary and secondary analyses. That is, significance for the secondary efficacy analysis will be declared only if the primary <i>P</i>-value is 0.05 or less, when the <i>p</i>-values are tested sequentially per the Hochberg method[2].</p>

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Section	Change or Revision						
Section 3.2.3	<p><b>Section Revised</b></p> <p><b>Deleted:</b></p> <ol style="list-style-type: none"><li>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).</li><li>Safety outcomes will be assessed by summary analysis of adverse events and clinical laboratory abnormalities.</li><li>Pharmacokinetic outcomes will be assessed by evaluating the population pharmacokinetics for CPP-1X (eflornithine) and sulindac.</li><li>Evaluate tissue and dietary polyamine levels.</li><li>Patient reported quality of life will be evaluated using HRQoL and patient utilities.</li><li>A pilot evaluation of an FAP-specific assessment, the time to the first FAP-related beneficent event, will be studied. This will involve analyzing the endoscopic polyposis data for regression of pre-colectomy colorectal polyposis, rectal/pouch polyposis, and regression of duodenal polyposis.</li><li>An analysis of the components and subgroups included in the primary analysis, and their contribution to the primary outcome.</li></ol> <p><b>Replaced with the following:</b></p> <p>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 Section 4 Populations for Analysis] wherever possible and will all be clearly noted as such.</p> <p>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.</p> <p>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 (see below).</p> <p>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).</p> <p>The subcategories of FAP events will be explored by disease stratum groups, and by Disease Site subgroups (see below). The subcategories of FAP events include:</p> <p><b>Table 3.1 Disease Site Subgroups</b></p> <table><tr><th>No</th><th>Group</th><th>Description</th></tr><tr><td>1</td><td>Disease Progression Indicating Need for Colectomy with IRA or Total Procto-Colectomy</td><td>Applies only to subjects with FAP surgical status of pre-colectomy (field name: DIAGSXST, code 1)</td></tr></table>	No	Group	Description	1	Disease Progression Indicating Need for Colectomy with IRA or Total Procto-Colectomy	Applies only to subjects with FAP surgical status of pre-colectomy (field name: DIAGSXST, code 1)
No	Group	Description					
1	Disease Progression Indicating Need for Colectomy with IRA or Total Procto-Colectomy	Applies only to subjects with FAP surgical status of pre-colectomy (field name: DIAGSXST, code 1)					

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Section	Change or Revision		
	2	Excisional intervention by surgical snare or trans-anal excision to remove any polyp $\geq 10$ mm in size (per pathology report) and/or pathologic evidence of high grade dysplasia	Excisional intervention does not apply to subjects with FAP surgical status of colectomy with ileostomy (field name: DIAGSXST, code 4) or subjects with FAP surgical status of pre colectomy (field name: DIAGSXST, code 1). For all remaining subjects, all $>5$ mm polyps must have been removed at baseline also  High grade dysplasia does not apply to subjects with FAP surgical status of colectomy with ileostomy (field name: DIAGSXST, code 4)
	3	Disease Progression Indicating Need for Proctectomy	Does not apply to subjects with FAP surgical status of proctocolectomy with ileal pouch anastomosis (IPAA) (field name: DIAGSXST, code 3) or FAP surgical status of colectomy with ileostomy (field name: DIAGSXST, code 4)
	4	Disease Progression Indicating Need for Pouch resection	Does not apply to subjects with FAP surgical status of pre colectomy (field name: DIAGSXST, code 1). or FAP surgical status of colectomy with ileostomy (field name: DIAGSXST, code 4) or FAP surgical status of colectomy with ileorectal anastomosis (IRA) (field name: DIAGSXST, code 2)
	5	Development of cancer in rectum or pouch	Does not apply to subjects with FAP surgical status of colectomy with ileostomy (field name: DIAGSXST, code 4)
	6	Progression in Spigelman Stage to more advanced stage (Stage 2, 3, 4)	Does not apply to subjects without duodenum (determined by abdominal surgical procedure of duodenectomy, duodenohepatojejunostomy, or Whipple procedure (field name SXPROC) and screening/baseline upper GI endoscopy not done (field name UGIND, Boolean data type)
	7	Disease Progression indicating need for excisional intervention (sub-mucosal resection, trans-duodenal excision, duodenectomy, ampullectomy, Whipple procedure)	Does not apply to subjects without duodenum (determined by abdominal surgical procedure of duodenectomy, duodenohepatojejunostomy, or Whipple procedure (field name SXPROC) and screening/baseline upper GI endoscopy not done (field name UGIND, Boolean data type)

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Section	Change or Revision	
	8	Development of cancer in duodenum
		Does not apply to subjects without duodenum (determined by abdominal surgical procedure of duodenectomy, duodenohepatectomy, or Whipple procedure (field name SXPDOC) and screening/baseline upper GI endoscopy not done (field name UGIND, Boolean data type)
	9	Spigelman stage (no progression)
		Does not apply to subjects without duodenum (determined by abdominal surgical procedure of duodenectomy, duodenohepatectomy, or Whipple procedure (field name SXPDOC) and screening/baseline upper GI endoscopy not done (field name UGIND, Boolean data type)
	10	>= 10 mm polyp in rectum pouch
		Does not apply to subjects with FAP surgical status of colectomy with ileostomy (field name: DIAGSXST, code 4) or subjects with FAP surgical status of pre colectomy (field name: DIAGSXST, code 1). For all remaining subjects, all >5 mm polyps must have been removed at baseline.
	11	High grade dysplasia (rectum-pouch)
		Does not apply to subjects with FAP surgical status of colectomy with ileostomy ((field name: DIAGSXST, code 4)
<p>These subcategories will be analyzed within the assigned disease strata (i.e. assigned at time of randomization). Separately, they will be analyzed by Disease Site, according to the concept of “the patient as a whole” meaning that <i>all known disease sites will be considered</i> because patients more often than not have more than one diseased organ system. For example, a patient randomized to treatment in the Duodenal Polyposis stratum who is also known to have colonic polyps will appear in the analyses for both Disease Site subgroups (Duodenal and Colonic). The total number of patients in the Duodenal Disease Site subgroup will include, for example, all patients randomized in the Duodenal Polyposis stratum + all other patients with known duodenal disease (irrespective of whether they have rectal/pouch disease). A similar approach will be taken for the Rectum/Pouch Polyposis group and Pre-colectomy strata.</p> <p>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.</p> <p>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.</p>		

**Study ID: CPP FAP-310, 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)**

**Summary of SAP Changes Ver. 5.0, April 2, 2018 to Ver. 5.1, July 30, 2018**

Section	Change or Revision
	<p>Patient reported health related quality of life measures will be evaluated using HRQoL (see Section 5.6 Health Related Quality of Life (HRQoL) Statistical Methods for more details).</p> <p>Tissue and dietary polyamine levels, as collected at patient study visits will be analyzed together with the results of the dietary questionnaires (see Section 5.7 Dietary Assessment) and related to treatment group and study outcomes.</p> <p>Safety outcome data and analyses are described in Section 5.5.5 Assessment of Toxicities.</p>
<b>Sec. 5.1</b>	<p><b>After 2<sup>nd</sup> paragraph, changed from:</b> “For the purposes of power calculations, we assume the following:”</p> <p><b>To:</b> Section header 5.2 Power Calculation Assumptions.</p> <p><b>After 2<sup>nd</sup> paragraph on section 5.2, added Section header:</b> 5.3 Hazard Rates</p> <p>Renumbered all following subsections in Section 5.</p>
<b>Sec. 5.4</b> (updated number)	<p><b>Deleted:</b> ”and Clinical Events Committee (CEC)”</p> <p><b>Renamed section header 5.4.1 from:</b> DMC <b>To:</b> DMC General Information</p> <p><b>After 4<sup>th</sup> paragraph from 5.4.1, Added section header:</b> 5.4.2 Prespecified Interim Efficacy and Futility Analysis</p>
<b>Sec. 5.4.2</b>	<p><b>6<sup>th</sup> paragraph, revised first sentence, from:</b> “The details of the efficacy and futility analysis are provided in Table 5.1 below presents a schematic diagram of the procedure. Also Table 5.2...”</p> <p><b>To:</b> “The details of the efficacy and futility analysis are provided in <u>Table 5.1 below which presents</u> a schematic diagram of the procedure. <u>Also</u> Table 5.2...”</p>
<b>5.5.3</b>	<p><b>Added sentence to 4<sup>th</sup> paragraph:</b> “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.”</p>
<b>End</b>	

**Study ID: CPP FAP-310, 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)**

**Summary of SAP Changes Ver. 5.1, July 30, 2018 to 5.2 January 25, 2019**

<b>Section</b>	<b>Change or Revision</b>
<b>Global</b>	<p><b>Changed</b> version Ver. 5.1, July 30, 2018 to January 25, 2019</p> <p><b>Updated:</b> Table of Contents, reference numbers, table numbers, and section numbers as required.</p>
<b>Sec. 3.2</b>	<p><b>Changed section title:</b></p> <p><b>From:</b> 3.2 Study Objectives and Primary Hypothesis Testing</p> <p><b>To:</b> 3.2 Study Objectives</p>
<b>Sec. 3.2.1</b>	<p><b>Added sub-section:</b></p> <p>3.2.1 Primary Analysis</p> <p>The primary analysis will be a time-to-event analysis using the stratified log-rank test. Graphical analyses (log-minus-log plots) will be used to check the assumption of constant hazard ratios with the COX model. See Section 7.3 below for further details of the calculation of the stratified log-rank statistic. The strata are the patient's sites of disease involvement at baseline, which is determined prior to randomization, and are: Rectal/pouch polyposis, Duodenal polyposis, and Precolectomy.</p> <p>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[8]. Additional analyses involving the overall 3-treatment group comparison and use of additional study populations (see Section 4.) for the two pairwise treatment comparisons, will be performed as supplemental analyses. Refer to section 5.5.3 for further details.</p>
<b>Section 3.2.3</b>	<p><b>Added the following sentence at the end of the section:</b></p> <p>Further analyses of the secondary endpoints may be conducted to evaluate and provide additional evidence to support its validity and confirm its clinical relevance.</p>
<b>End</b>	

**Study ID: CPP FAP-310, 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)**

**Summary of SAP Changes Ver. 5.1, July 30, 2018 to 5.2 January 25, 2019**

Section	Change or Revision
<b>Global</b>	<b>Changed</b> version Ver. 5.1, July 30, 2018 to January 25, 2019 <b>Updated:</b> Table of Contents, reference numbers, table numbers, and section numbers as required.
<b>Sec. 3.2</b>	<b>Changed section title:</b> <b>From:</b> 3.2 Study Objectives and Primary Hypothesis Testing <b>To:</b> 3.2 Study Objectives
<b>Sec. 3.2.1</b>	<b>Added sub-section:</b> 3.2.1 Primary Analysis The primary analysis will be a time-to-event analysis using the stratified log-rank test. Graphical analyses (log-minus-log plots) will be used to check the assumption of constant hazard ratios with the COX model. See Section 7.3 below for further details of the calculation of the stratified log-rank statistic. The strata are the patient's sites of disease involvement at baseline, which is determined prior to randomization, and are: Rectal/pouch polyposis, Duodenal polyposis, and Precolectomy.  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[8]. Additional analyses involving the overall 3-treatment group comparison and use of additional study populations (see Section 4.) for the two pairwise treatment comparisons, will be performed as supplemental analyses. Refer to section 5.5.3 for further details.
<b>Section 3.2.3</b>	<b>Added the following sentence at the end of the section:</b>  Further analyses of the secondary endpoints may be conducted to evaluate and provide additional evidence to support its validity and confirm its clinical relevance.
<b>End</b>	