1. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Cancer Prevention Pharmaceuticals, Inc.</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier
Volume:
Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
CPP-1X (eflornithine) and sulindac combination</td></tr>
<tr><td>Name of Active Ingredient:
Eflornithine HCl monohydrate/sulindac</td></tr>
<tr><td colspan="3">Title of Study: A Double-Blind, Randomized, Phase 3 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)</td></tr>
<tr><td colspan="3">Co-Principal Investigators:
Carol Burke, MD and James Church, MD, FACS, FASCRS (Cleveland Clinic, Cleveland, OH), Jewell Samadder, MD (Mayo Clinic-Phoenix Campus, Phoenix, AZ), Ernest T. Hawk, MD, MPH (Department of Clinical Cancer Prevention, Division of OVP, The University of Texas MD Anderson Cancer Center, Houston, TX), and Prof. Dr. Med Gabriella Möslein (Witten-Herdecke University, Wuppertal, Germany)
Investigators: Multicenter, see Appendix 16.1.4.</td></tr>
<tr><td colspan="3">Study Centers: This study was conducted at 17 sites in the United States, Canada, Belgium, Germany, the Netherlands, Spain, and the United Kingdom.</td></tr>
<tr><td colspan="3">Publication (Reference): Burke CA, Dekker E, Jewel Samadder N, Stoffel E, Cohen A. BMC Gastroenterology;2016;16:87.</td></tr>
<tr><td colspan="2">Study Period (Years):
Date first subject enrolled: 02 December 2013
Date last subject completed: 12 November 2018</td><td>Phase of development: 3</td></tr>
<tr><td colspan="3">Objectives: This randomized, double-blind, Phase 3 study compared the efficacy, safety, and pharmacokinetics of the CPP-1X (eflornithine hydrochloride [HCl])/sulindac combination vs. CPP-1X and sulindac as single agents, with up to a 48-month maximum treatment period in subjects with FAP.
The primary objective of this study was 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.</td></tr>
</table>

Methodology: This was a Phase 3, double-blind, randomized study in adult subjects with FAP who had a confirmed adenomatous polyposis coli (APC) mutation. If a subject had prior colorectal surgery, ≥3 years must have elapsed since colectomy/proctocolectomy with ileal-rectal anastomoses (IRA) or pouch.

After signing the informed consent form, eligible subjects were randomized into 1 of 3 treatment groups in a 1:1:1 ratio (CPP-1X 750 mg + sulindac 150 mg: CPP-1X placebo + sulindac 150 mg: CPP-1X 750 mg + sulindac placebo) and stratified by FAP-related time to first event prognosis: (best [ie, longest projected time to first FAP-related event – rectal/pouch polyposis], intermediate [duodenal polyposis], and worst [pre-colectomy]) using an interactive web-based system.

Subjects received study drug once daily for 24 months and, based on date of randomization, were offered continued receipt of blinded study drug for up to a total of 36, 42, or 48 months until one of the following occurred: 1) subject had an FAP-related event or prematurely discontinued study drug for another reason or 2) all randomized subjects reached a minimum of 24, 36, 42, or 48 months of treatment.

FAP-related events varied by disease site and were defined as: 1) FAP-related excisional intervention of polyps ≥10 mm involving the rectum or pouch, and/or 2) progression to more advanced duodenal polyposis (Spigelman stage progression 2, 3, or 4) and/or 3) clinically important events, which included disease progression indicating the need for excisional intervention/surgery, cancer, or death. Follow-up of the subject for FAP-related surgeries continued, per protocol, between 1 and 6 months after the last dose of study drug.

A Data Monitoring Committee (DMC) oversaw the performance and safety conduct of this study. The DMC consisted of 5 members (4 medical doctors and 1 statistician as voting members) who received confidential reports on a periodic basis. The DMC was responsible for decisions regarding possible termination of the study for futility or safety reasons. The prespecified interim efficacy and futility analysis was conducted in a blinded manner. The analysis was performed after a total of 45 primary endpoints occurred (or as soon as possible thereafter), which represented 50% of the expected maximum study information. After reviewing the analysis results, the DMC provided recommendations to Cancer Prevention Pharmaceuticals, Inc. (CPP) regarding possible termination of the study for either futility, efficacy, or safety reasons. The DMC found no reason to stop the study based on this interim analysis.

Number of Subjects (Planned and Analyzed):

Fifty subjects per treatment group were planned. One hundred seventy-one subjects (56 CPP-1X + sulindac, 58 CPP-1X [placebo] + sulindac, 57 CPP-1X + sulindac [placebo]) were randomized and included in the Intent-to-Treat (ITT) Population; 169 subjects (56 CPP-1X + sulindac, 57 CPP-1X [placebo] + sulindac, 56 CPP-1X + sulindac [placebo]) received at least 1 dose of study drug and were included in the Safety Population; and 147 subjects (47 CPP-1X + sulindac, 48 CPP-1X [placebo] + sulindac, 52 CPP-1X + sulindac [placebo]) fulfilled all protocol eligibility, intervention, and outcome assessments and were included in the Per-Protocol Population.

Diagnosis and Main Criteria for Inclusion: Male and female subjects ≥18 years of age with a diagnosis of phenotypic classical FAP with disease involvement of the duodenum and/or colon/rectum/pouch, APC mutation (with or without family history), and classical FAP phenotype (hundreds to thousands of colorectal adenomatous polyps) were eligible for the study. Upper gastrointestinal endoscopy/lower gastrointestinal (LGI) endoscopy (proctoscopy/colonoscopy) must have been performed within 30 days of randomization. Subjects had either an intact colon/rectum and prophylactic surgery was being considered, rectal/pouch polyposis (if prior colorectal surgery, at least 3 years since colectomy/proctocolectomy with IRA or pouch), or duodenal polyposis.

Test Product, Dose and Mode of Administration, Batch Number:

CPP-1X (eflornithine HCl) 750 mg (three 250-mg tablets) + sulindac 150 mg (one 150-mg tablet); oral; lot numbers for CPP-1X: 40398, 40507, 40635, 40726, and 40783; lot numbers for sulindac: 40399, 40496, 40539, 40645, 40667, 40725, 40760, 40784, and 40828

Duration of Treatment: Subjects enrolled before protocol version 4.0 received up to 24 months of treatment with study drug. Two protocol amendments allowed treatment extension. The first was implemented in protocol version 4.0 (14 March 2016) and allowed for an additional 12 months of treatment (up to 36 months). The second extension was implemented in protocol version 5.0 (21 July 2017), as follows:

Subjects completing 24 months of study drug without an FAP-related event may have continued receiving study drug 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 occurred:

1. Subject had an FAP-related event or prematurely discontinued study drug for other reasons
2. Study end date of 30 April 2019 was reached
3. 90 FAP-related events occurred
4. Less than 90 FAP-related events occurred prior to 30 April 2019 and an earlier study end date was set by CPP and reviewed by the DMC
5. A study end date prior to 30 April 2019 was recommended by the DMC for safety reasons and approved by CPP

Reference Therapy, Dose and Mode of Administration, Batch Number:

CPP-1X placebo tablets (3 tablets) and sulindac placebo tablet (1 tablet); oral; lot numbers for CPP-1X placebo: 40398, 40507, 40635, 40726, and 40783; lot numbers for sulindac placebo: 40399, 40496, 40539, 40645, 40667, 40725, 40760, 40784, and 40828

Criteria for Evaluation:

Efficacy: The primary efficacy variable was the time from the date of randomization to the date of the first occurrence of any FAP-related event. Baseline disease evaluation included assessment of the colon, rectum, or neo-rectum (ileal pouch) by colonoscopy or flexible sigmoidoscopy and duodenal assessment. At 6-month intervals, subjects underwent repeat upper and lower endoscopy. FAP-related events by disease site were as follows:

1. Preoperative, intact colon:
   - Disease progression indicating need for colectomy with IRA or total proctocolectomy
2. Rectum or pouch events included one or more of the following:
   a. Excisional intervention by surgical snare or trans-anal excision to remove any polyp ≥10 mm in size (per pathology report) and/or pathologic evidence of high-grade dysplasia. For subjects stratified to the duodenal group, all concurrent rectal pouch polyps >5 mm must have been removed at baseline for this event to apply.
   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 included the following:
   a. Progression in Spigelman stage to a more advanced stage (Stage 2, 3, or 4)
   b. Disease progression indicating need for excisional intervention (sub-mucosal resection, trans-duodenal excision, ampullectomy, duodenectomy, Whipple procedure)
   c. Development of cancer in duodenum
   d. Death

Excisional intervention may have included open surgery, trans-anal surgery, or endoscopic excisions/snare, but did not include cautery ablations or hot biopsy. Disease progression was based on endoscopic evaluations compared with baseline that demonstrated 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.

Pharmacokinetics: All subjects had blood samples obtained for pharmacokinetic analyses at the Month 3 Visit. Pharmacokinetic analysis results are provided in Appendix 16.1.13.1.

Pharmacogenomics: All subjects had a sample of peripheral blood collected at screening/baseline for pharmacogenomic and genetic testing. Pharmacogenetic analysis results are provided in Appendix 16.1.13.2.

Urine Polyamine Analysis: Subject urine samples were collected and analyzed for polyamine content at screening/baseline and at each endoscopy/proctoscopy evaluation. Analyses of urinary polyamines in relation to treatment group and outcome are provided in Appendix 16.1.13.3.

Health-Related Quality of Life: Quality-of-life questionnaires (European Organisation for Research and Treatment of Cancer [EORTC] quality-of-life questionnaire (QLQ)-C30, EORTC QLQ-CR29, EuroQol-5D (EQ-5D), and the modified Cancer Worry Scale) were provided to the subject to complete at baseline, Month 3, every 6 months beginning with Month 6, and at end of treatment. At baseline, every 12 months, and end of treatment, subjects at sites in the United States and Canada completed the Food Frequency Questionnaire (FFQ). Analyses of health-related quality-of-life results are provided in Appendix 16.1.13.4.

Safety: Safety was assessed by adverse events, laboratory evaluations (complete blood count, chemistry panel, and urinalysis), physical examinations, vital signs, desmoids, electrocardiogram, ototoxicity risk (air conduction audiometry for hearing impairment and clinical assessment for ototoxicity adverse event symptoms), and gastrointestinal evaluations (including subject diaries used to record symptoms and clinical assessment for gastrointestinal adverse event symptoms).

Statistical Methods:

Based on advice provided by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA), the 2 primary 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) were performed sequentially as part of the primary analysis, each at the 2-sided p=0.05 level. The primary analysis was a time-to-event analysis using the stratified log-rank test. The primary result for the study was the stratified log-rank test. Graphical analyses (log-minus-log plots) were used to check the assumption of constant hazard ratios with the Cox model. The strata were based on the FAP-related time to first event prognosis by area of disease involvement for each subject, as determined prior to randomization, and were: rectal/pouch polyposis, duodenal polyposis, and pre-colectomy.

Time-to-event curves were displayed using the method of Kaplan and Meier. Analyses involving the overall 3-treatment group comparison and use of additional study populations for the 2 pairwise treatment comparisons were performed as supplemental analyses.

The overall type I error for the secondary efficacy analysis was controlled using the Hochberg step-up method for multiple comparisons. The primary analysis served 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 was declared only if the primary p-value was ≤0.05, when the p-values were tested sequentially per the Hochberg method.

Exploratory (i.e., post hoc) analyses were also performed for the primary endpoint: analysis censoring Spigelman progressions only; analysis censoring Spigelman progressions and polyps ≥10 mm in size (per pathology report) and/or pathologic evidence of high-grade dysplasia in the rectum or pouch; and analysis of LGI FAP-related events in subjects with an intact colon, rectum, and/or ileal pouch.

Secondary endpoints were Upper Gastrointestinal Observed Improvement (UGIOI) and Lower Gastrointestinal Observed Improvement (LGIOI). These endpoints independently summarized the corresponding 6- and 12-month investigator scores according to whether or not there was any positive improvement at either Month 6 (compared to baseline) or Month 12 (compared to baseline or Month 6), under the condition that there be no worsening at either time point (compared to the preceding time point). These binary UGIOI and LGIOI secondary efficacy endpoints were compared in a manner similar to the primary analysis, using the same 2 primary treatment comparisons and conditioning on the 3 disease site strata (rectum/pouch polyposis, duodenal polyposis, pre-colectomy).

The CPP-1X + sulindac, CPP-1X (placebo) + sulindac, and CPP-1X + sulindac (placebo) treatment groups are referred to as the combination, sulindac, and CPP-1X treatment groups, respectively.

SUMMARY – CONCLUSIONS

This synopsis reports results regarding disposition, demographic and baseline characteristics, the primary efficacy endpoint, and safety evaluations.

The final decision concerning the study end date was based on accrued FAP-related primary endpoints, number of subjects still active in the study, FAP-related event projections, and additional safety reviews. In May 2018, CPP decided to complete all final subject visits by the end of November 2018. This decision was based on many factors, including a significant slowing in the number of reported FAP-related events and statistical projections with 49 remaining subjects on study. The DMC was consulted and had no safety concerns or objections to this plan.

Disposition and Demographic and Baseline Characteristics:

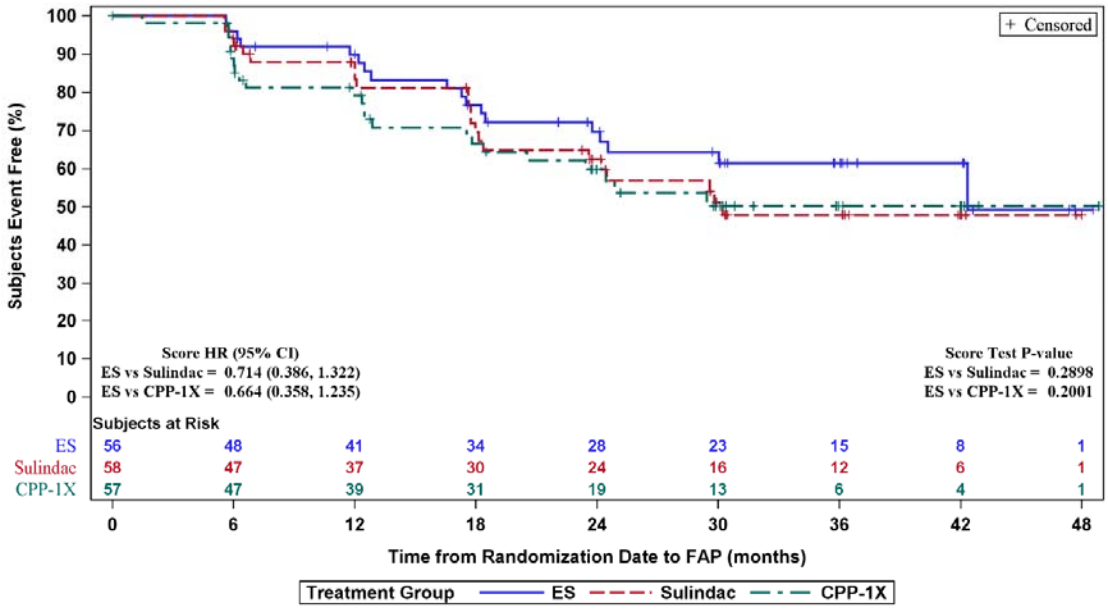
A total of 250 subjects enrolled in the study and 169 subjects (56 combination, 57 sulindac, 56 CPP-1X) received at least 1 dose of study drug. The median time in the treatment period was 23.4 months (24.3 months combination, 18.5 months sulindac, 21.9 months CPP-1X). Sixty-three (36.8%) subjects completed the study due to experiencing an FAP-related event. The most common reason for not completing the study was adverse event (19 subjects; 11.1%). The majority of subjects (88.9%) completed 30 days of off-treatment follow-up.

Baseline disease characteristics were generally similar across the treatment groups. The duodenal polyposis disease stratum was the largest cohort (58.5%), followed by pre-colectomy (21.6%) and rectal/pouch polyposis (19.9%). Overall, mean time since diagnosis of FAP was 17.5 years.

Efficacy Results:

The percentage of subjects with an FAP-related event was 32.1% (18 of 56) in the combination treatment group, 37.9% (22 of 58) in the sulindac treatment group, and 40.4% (23 of 57) in the CPP-1X treatment group. Results of the primary analysis with the ITT Population are shown in the figure below. This analysis evaluated 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 prespecified primary endpoint was a composite endpoint of a spectrum of event types. The hazard ratio for the combination vs. sulindac was 0.71 (95% confidence interval [CI]: 0.4, 1.3) with a nonsignificant p-value of 0.2898; for the combination vs. CPP-1X, the hazard ratio was 0.66 (95% CI: 0.4, 1.2) with a nonsignificant p-value of 0.2001.

Time from Randomization to First Occurrence of Any FAP-Related Event (ITT Population)

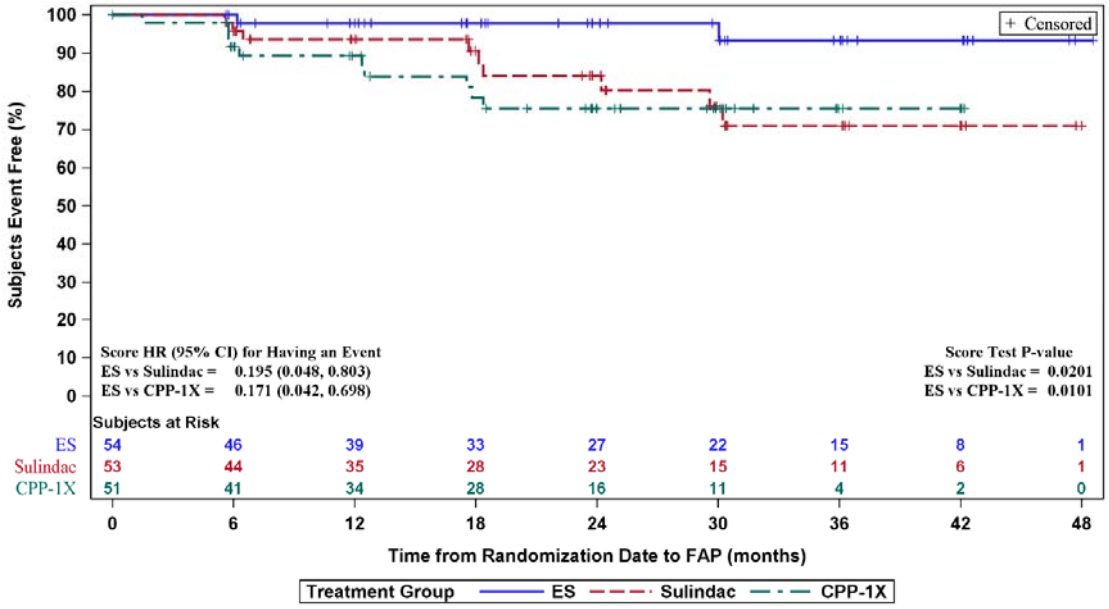


CI=confidence interval; ES=CPP-1X (eflornithine) + sulindac; FAP=familial adenomatous polyposis; HR=hazard ratio; ITT=Intent-to-Treat

Although no statistically significant difference between the combination treatment group and either single-agent treatment group was observed in the prespecified analyses of the primary endpoint by disease stratum group (pre-colectomy, duodenal polyposis, and rectal/pouch polyposis), results suggested that the combination may have greater efficacy than either single agent in subjects in the pre-colectomy stratum.

An exploratory analysis of the primary endpoint was performed evaluating FAP-related events in the functional lower GI anatomy that excluded 13 subjects with colectomy and ileostomy; results are shown in the figure below. This analysis included subjects with an intact colon, rectum, and/or ileal pouch; therefore, disease progression or drug effect could be evaluated in these LGI sites. The percentage of subjects with an FAP-related event was 3.7% (2 of 54) in the combination treatment group, 17.0% (9 of 53) in the sulindac treatment group, and 19.6% (10 of 51) in the CPP-1X treatment group. The hazard ratio was 0.20 (95% CI: 0.0, 0.8; p=0.0201) for the combination vs. sulindac and 0.17 (95% CI: 0.0, 0.7; p=0.0101) for the combination vs. CPP-1X.

Time from Randomization to First Occurrence of Any FAP-Related LGI Event in Subjects with LGI Anatomy (ITT Population Excluding Subjects with Colectomy and Ileostomy)



CI=confidence interval; ES=CPP-1X(eflornithine) + sulindac; FAP=familial adenomatous polyposis; HR=hazard ratio; ITT=Intent-to-Treat; LGI=lower gastrointestinal

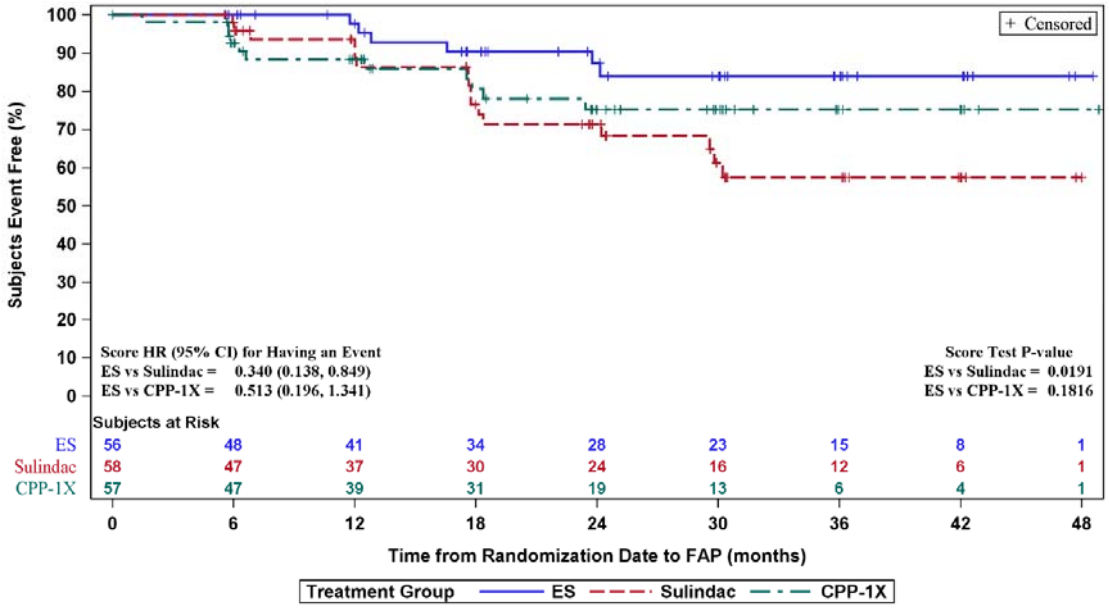
The prespecified definition of an FAP-related event included 2 events that indicate a change in disease severity (excisional intervention by surgical snare or trans-anal excision to remove any polyp ≥10 mm in size and/or pathologic evidence of high-grade dysplasia and Spigelman stage progression). These 2 events are not considered clinically meaningful by either the FDA (excision of ≥10 mm rectal or pouch polyp) or EMA (Spigelman progression).

In an exploratory analysis of FAP-related gastrointestinal events that censored subjects who had excision of a polyp in the rectum or pouch ≥10 mm with or without high grade dysplasia, the percentage of subjects with an FAP-related LGI event was 0% (0 of 54) in the combination treatment group, 13.2% (7 of 53) in the sulindac treatment group, and 15.7% (8 of 51) in the CPP-1X treatment group. The hazard ratio was 0.000 (p=0.0048) for the combination vs. sulindac and 0.000 (p=0.0031) for the combination vs. CPP-1X.

In an exploratory analysis of the primary endpoint that censored the 22 subjects with Spigelman stage progression alone without any Spigelman stage progression-related surgeries, the percentage of subjects with an FAP-related event was 16.1% (9 of 56) in the combination treatment group, 32.8% (19 of 58) in the sulindac treatment group, and 22.8% (13 of 57) in the CPP-1X treatment group. The hazard ratio was 0.43 (95% CI: 0.2, 0.9; p=0.0304) for the combination vs. sulindac and 0.63 (95% CI: 0.3, 1.5; p=0.2894) for the combination vs. CPP-1X.

In an exploratory analysis of the primary endpoint that censored subjects with an FAP-related endpoint of Spigelman stage progression (if occurred alone) or excision of a polyp in the rectum or pouch ≥10 mm with or without high grade dysplasia, the percentage of subjects with an FAP-related event was 10.7% (6 of 56) in the combination treatment group, 27.6% (16 of 58) in the sulindac treatment group, and 19.3% (11 of 57) in the CPP-1X treatment group. As shown in the figure below, the hazard ratio was 0.34 (95% CI: 0.1, 0.8; p=0.0191) for the combination vs. sulindac and 0.51 (95% CI: 0.2, 1.3; p=0.1816) for the combination vs. CPP-1X.

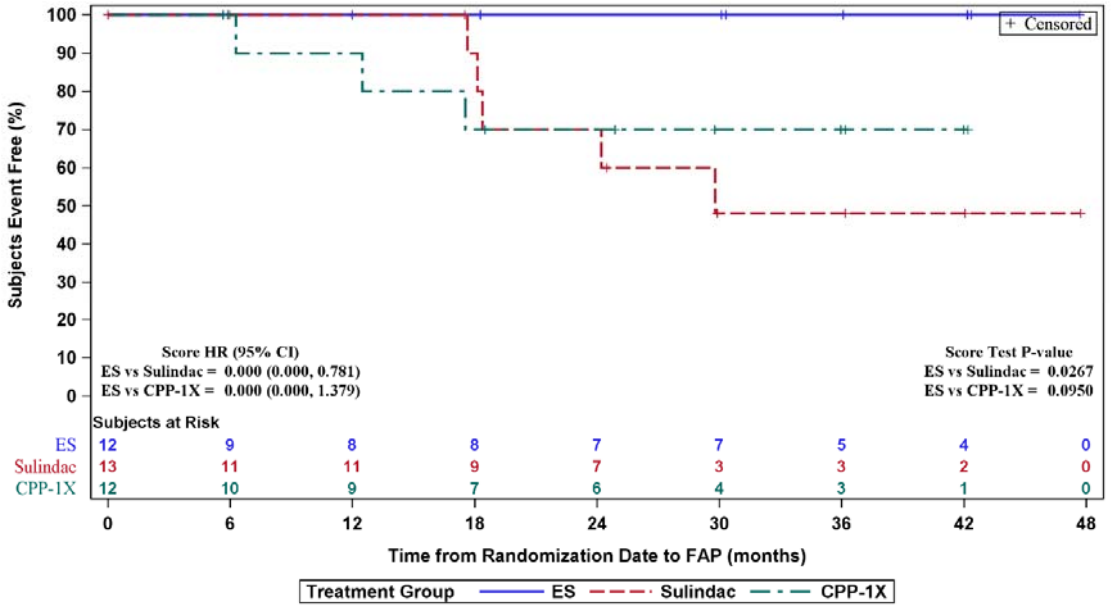
Time from Randomization to First Occurrence of Any FAP-Related Event (ITT Population Censoring Excision of ≥10 mm Polyps and Spigelman Stage Progression if Occurred Alone)



CI=confidence interval; ES=CPP-1X (eflornithine) + sulindac; FAP=familial adenomatous polyposis; HR=hazard ratio; ITT=Intent-to-Treat

A post hoc analysis was performed in the pre-colectomy stratum that censored Spigelman stage progression alone without any Spigelman stage progression-related surgeries. Results are shown in the figure below. The percentage subjects with an FAP-related event was 0% (0 of 12) in the combination treatment group, 38.5% (5 of 13) in the sulindac treatment group, and 25.0% (3 of 12) in the CPP-1X treatment group. The hazard ratio was 0.000 (95% CI: 0.000, 0.781; p=0.0267) for the combination vs. sulindac and 0.000 (95% CI: 0.000, 1.379; p=0.0950) for the combination vs. CPP-1X.

Time from Randomization to First Occurrence of Any FAP-Related Event (ITT Population – Pre-Colectomy Stratum Censoring 5 Subjects with Spigelman Stage Progression Alone Without Any Spigelman Stage Progression-Related Surgeries)



CI=confidence interval; ES=CPP-1X (eflornithine) + sulindac; FAP=familial adenomatous polyposis; HR=hazard ratio; ITT=Intent-to-Treat

Safety Results: The overall summary of adverse events is presented below.

Summary of Adverse Events - Safety Population

	Combination N=56	Sulindac N=57	CPP-1X N=56
Subjects with:	**n (%) of Subjects**		
Any TEAE	52 (92.9)	50 (87.7)	49 (87.5)
A treatment-related TEAE[a]	38 (67.9)	42 (73.7)	31 (55.4)
A TEAE Grade 3 or higher	12 (21.4)	12 (21.1)	17 (30.4)
An SAE	11 (19.6)	11 (19.3)	14 (25.0)
A treatment-related SAE	3 (5.4)	4 (7.0)	1 (1.8)
An adverse event leading to discontinuation of study drug	9 (16.1)	6 (10.5)	5 (8.9)
An adverse event leading to death	0	0	0

SAE=serious adverse event; TEAE=treatment-emergent adverse event
[a] Considered to be possibly, probably, or definitely related to study drug by the investigator.

Treatment-emergent adverse events experienced by ≥10.0% of subjects were nausea (21.4%), abdominal pain (14.3%), upper respiratory tract infection (14.3%), headache (14.3%), diarrhea (12.5%), rectal hemorrhage (12.5%), abdominal pain upper (12.5%), gastroenteritis (12.5%), vomiting (10.7%), hematochezia (10.7%), nasopharyngitis (10.7%), and rash (10.7%) in the combination treatment group; nausea (21.1%), headache (19.3%), vomiting (17.5%), abdominal pain (14.0%), fatigue (14.0%), upper respiratory tract infection (14.0%), rectal hemorrhage (12.3%), tinnitus (10.5%), diarrhea (10.5%) in the sulindac treatment group; and nasopharyngitis (17.9%), nausea (16.1%), diarrhea (14.3%), fatigue (14.3%), vomiting (12.5%), hematochezia (10.7%), dizziness (10.7%), and cough (10.7%) in the CPP-1X treatment group.

The majority of subjects experienced TEAEs that were at most mild or moderate in severity. Treatment-emergent adverse events grade 3 or higher experienced by >1 subject in any treatment group were small intestinal obstruction (2 [3.6%] subjects in the combination treatment group and 2 [3.5%] subjects in the sulindac treatment group), ileus (2 [3.6%] subjects in the CPP-1X treatment group), ligament rupture (2 [3.6%] subjects in the combination treatment group), and depression (2 [3.5%] subjects in the sulindac treatment group.

The most common treatment-related TEAEs were nausea (16.1%), rash (10.7%), and abdominal pain upper (8.9%) in the combination treatment group; nausea (15.8%), headache (12.3%), and tinnitus (8.8%) in the sulindac treatment group; and nausea (14.3%), diarrhea (8.9%), vomiting (8.9%), and headache (8.9%) in the CPP-1X treatment group.

The majority of SAEs were considered unrelated to study drug by the investigator. Three (5.4%) subjects in the combination treatment group (nephritis, psychotic disorder, and pancreatitis acute, respectively), 4 (7.0%) subjects in the sulindac treatment group (nausea, deep vein thrombosis, depression, and abortion spontaneous, respectively), and 1 (1.8%) subject in the CPP-1X treatment group (cerebrovascular accident) experienced treatment-emergent SAEs considered at least possibly related to study drug.

Hypersensitivity (2 [3.6%] subjects in the combination treatment group group) was the only TEAE that led to premature discontinuation of study drug in >1 subject in a treatment group.

Evaluation of adverse events of special interest (cardiovascular/thrombotic, anaphylactic reaction, gastrointestinal, hearing, hematopoietic cytopenias, depression), which are known toxicities of sulindac and/or eflornithine, as well as malignancies, did not identify any safety concern with the combination compared with those of either single agent.

No clinically concerning results were observed for hematology, chemistry, urinalysis, or vital sign results.

Ototoxicity was evaluated by TEAEs and by audiometry. The number of subjects experiencing clinical symptoms was small, with no significant increase in the combination treatment group compared to the single-agent treatment groups.

CONCLUSION:

No statistically significant difference was observed between the combination treatment group (CPP-1X 750 mg + sulindac 150 mg) and either single agent for the primary efficacy endpoint, time from the date of randomization to the date of the first occurrence of any FAP-related event in the subject as a whole. However, analyses suggested that the combination may have greater efficacy than either single agent in subjects in the pre-colectomy stratum, and a post hoc analysis demonstrated the superiority of the combination treatment group compared with either single agent for time to first FAP-related LGI event.

To maximize the number of FAP-related events detected during the study, CPP included excisional events (polyps ≥10 mm in the rectum or pouch) as well as Spigelman progressions that were not associated with any surgical procedure, events that are not considered clinically meaningful by either

the FDA or EMA. Post hoc analysis of data that excluded these events provides statistically significant support for the efficacy of the combination of CPP-1X 750 mg + sulindac 150 mg.

Safety data from this study do not indicate any safety concerns with the combination over either of the approved constituents of the combination.

Date of the report: Draft 20 November 2019