24 June 2021
EMA/CHMP/244212/2021
Committee for Medicinal Products for Human Use (CHMP)

# Withdrawal assessment report

## Flynpovi

International non-proprietary name: eflornithine / sulindac

Procedure No. EMEA/H/C/005043/0000

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# Administrative information

| | |
|---|---|
| Name of the medicinal product: | Flynpovi |
| Applicant: | Cancer Prevention Pharma (Ireland) Limited<br>70 Sir John Rogerson's Quay<br>Dublin 2<br>IRELAND |
| Active substance: | Eflornithine hydrochloride / sulindac |
| International Non-proprietary Name/Common Name: | eflornithine / sulindac |
| Pharmaco-therapeutic group (ATC Code): | Not yet assigned |
| Therapeutic indication(s): | Flynpovi is indicated as an adjunct to standard of care endoscopic surveillance for delaying the need for major surgery or resection of advanced adenoma in adult patients with familial adenomatous polyposis (FAP). |
| Pharmaceutical form(s): | Film-coated tablet |
| Strength(s): | 288.6 mg / 75 mg |
| Route(s) of administration: | Oral use |
| Packaging: | blister (PVC/PCTFE/PVC/alu) |
| Package size(s): | 56 tablets |

# Table of contents

# List of abbreviations

| | |
|---|---|
| AE | adverse event |
| AEOSI | adverse events of special interest |
| APC | adenomatous polyposis coli |
| AUC | area under the concentration-time curve |
| BE | bioequivalence |
| CI | confidence interval |
| Cmax | maximum serum concentration |
| COX | cyclooxygenase |
| CPP-1X | eflornithine |
| CRA | colorectal adenomas |
| DFMO | Difluoromethylornithine or eflornithine |
| DSMB | Data and Safety Monitoring Board |
| E+S | eflornithine + sulindac |
| EC50 | half maximal effective concentration |
| Eflornithine | eflornithine hydrochloride (HCl) monohydrate |
| ES-FDC | eflornithine sulindac fixed-dose combination |
| FAP | familial adenomatous polyposis |
| FDA | Food and Drug Administration |
| FP | finished product |
| GC | gas Chromatography |
| GC-MS | gas chromatography mass spectrometry |
| GI | gastrointestinal |
| HPLC | high performance liquid chromatography |
| HR | hazard ratio |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IC50 | half maximal inhibitory concentration |
| IND | Investigational New Drug |
| InSIGHT | International Society for Gastrointestinal Hereditary Tumours |
| IPAA | ileal pouch-anal reconstruction |
| IR | infrared |
| IRA | ileorectal anastomosis |

| | |
|---|---|
| IRB | Institutional Review Board |
| ISE | Integrated Summary of Efficacy |
| ITT | intent-to-treat |
| LGIOI | lower gastrointestinal observed improvement |
| MCAR | missing completely at random |
| MNAR | missing not at random |
| MS | mass Spectrometry |
| N | no |
| NCI | National Cancer Institute |
| NIH | National Institutes of Health |
| NMR | Nuclear Magnetic Resonance |
| NSAID | nonsteroidal anti-inflammatory drug |
| NW | non-white |
| PPAR | peroxisome proliferator-activated receptor |
| PSCA | Pharmacoprevention of Sporadic Colorectal Adenomas |
| RR | risk ratio |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SSAT | spermidine/spermine N1-acetyltransferase |
| UGIOI | upper gastrointestinal observed improvement |
| US | United States |
| W | white |
| UV | Ultraviolet |
| XR(P)D | X-Ray (Powder) Diffraction |
| Y | yes |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Cancer Prevention Pharma (Ireland) Limited submitted on 29 May 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Flynpovi, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 April 2018.

Flynpovi, was designated as an orphan medicinal product EU/3/12/1086 on 24 January 2013 in the following condition: Treatment of familial adenomatous polyposis.

The applicant applied for the following indication:

Flynpovi is indicated as an adjunct to standard of care for treatment of adult patients with familial adenomatous polyposis (FAP) who have an intact colon, rectum, or ileo-anal pouch.

The effect of Flynpovi-induced reduction of polyp burden on the risk of intestinal cancer has not been demonstrated (see sections 4.4 and 5.1).

Usual medical care for FAP patients should be continued while taking Flynpovi.

**The legal basis for this application refers to:**

Article 10(b) of Directive 2001/83/EC – relating to applications for fixed combination products

The application submitted is a fixed combination medicinal product.

## *Information on Paediatric requirements*

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0419/2019 on the granting of a (product-specific) waiver.

## *Information relating to orphan market exclusivity*

## Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

## *Applicant's request(s) for consideration*

## Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation.

### *Protocol assistance*

The applicant received the following protocol assistance on the development relevant for the indication subject to the present application:

| **Date** | **Reference** | **SAWP co-ordinators** |
|---|---|---|
| 20 January 2011 | EMA/CHMP/SAWP/19232/2011 | Dr Ferran Torres, Dr Sif Ormarsdóttir and Prof. Brigitte Blöchl-Daum |
| 21 July 2011 | EMA/CHMP/SAWP/527837/2011 | Dr Pierre Demolis and Dr Ferran Torres |
| 21 May 2015 | EMA/CHMP/SAWP/301490/2015 | Dr Elmer Schabel, Dr Jens Ersbøll and Prof. Markku Pasanen |
| 23 June 2016 | EMA/CHMP/SAWP/403845/2016 | Dr Caroline Auriche and Dr Elmer Schabel |
| 22 March 2018 | EMA/CHMP/SAWP/151130/2018 | Dr Walter Janssens and Dr Juha Kolehmainen |
| 18 October 2018 | EMA/CHMP/SAWP/689338/2018 | Dr Walter Janssens and Dr Ewa Balkowiec-Iskra |
| 17 October 2019 | EMA/CHMP/SAWP/545137/2019 | Dr Elmer Schabel and Dr Andreas Kirisits |

The Protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

- The evaluation of the secondary endpoints in study CPP-FAP-310 using GCP or CLIA validated assays in CLIA accredited laboratories;
- The choice of API specifications for sulindac and eflornithine;
- The non-clinical package, in particular the need for additional carcinogenicity studies, reproductive and developmental studies to support the development of the eflornithine and sulindac combination;
- The design of drug-drug interaction, ADME, and bioavailability studies for the eflornithine and sulindac combination; the completeness of the clinical (food effect, renal impairment, and bioequivalence study and evaluation of enantiomers) and non-clinical (cytochrome P450 and renal and hepatic transporter studies) package for MAA;
- The completeness of the intended non-clinical (hERG results to assess cardiovascular safety) and clinical (paediatric protocol synopsis and measurement of enantiomers during the planned bioequivalence studies) package for MAA;
- The design aspects of the double-blind phase III trial CPP-301 for evaluating the safety and efficacy of the combination treatment of eflornithine and sulindac in the reduction of the number of colorectal polyps in patients with FAP;
- The amount of non-clinical and clinical evidence expected for a MAA;
- The likelihood, once the result of the CPP-FAP-310 trial become available, for the combination therapy to be granted a conditional marketing authorisation or an authorisation under exceptional circumstances;
- the proposed methodological approach to assess the treatment-related effects of the fixed-dose combination and the benefit/risk balance for the treatment of FAP patients.

## *1.2. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Peter Kiely Co-Rapporteur: Alexandre Moreau

| | |
|---|---|
| The application was received by the EMA on | 29 May 2020 |
| The procedure started on | 18 June 2020 |
| The Rapporteur's first Assessment Report was circulated to all CHMP members on | 8 September 2020 |
| The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on | 7 September 2020 |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on | 21 September 2020 |
| The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on | 15 October 2020 |
| The applicant submitted the responses to the CHMP consolidated List of Questions on | 21 January 2021 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on | 1 March 2021 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 11 March 2021 |
| The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on | 25 March 2021 |
| The applicant submitted the responses to the CHMP List of Outstanding Issues on | 18 April 2021 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on | 5 May 2021 |
| The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on | 19 May 2021 |
| The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Flynpovi on | 24 June 2021 |

# 2. Scientific discussion

## *2.1. Problem statement*

### 2.1.1. Disease or condition

FAP is an orphan disease in which affected patients develop hundreds to thousands of polyps in the gastrointestinal (GI) tract. Without treatment nearly 100% of patients will develop colorectal cancer at an early age (Vasen, et al., 2008).

FAP is most commonly caused by mutations/deletions in the adenomatous polyposis coli (APC) tumour suppressor gene, which is located on chromosome 5q21-22. Disease progression in patients with FAP occurs as a continuum across the patient's life span. FAP is characterised by the development of hundreds to thousands of adenomas in the colorectum usually beginning during childhood and in adolescence (Vasen, et al., 2008). Without surgical intervention, there is almost a 100% chance the adenomas will develop into colorectal cancer by the mean age of 40 to 50 years (Vasen, et al., 2008). Later in life, duodenal polyposis develops. The treatment of duodenal adenomas depends on the severity of the disease; if untreated, these progress to malignancy in approximately 5% of cases (Vasen, et al., 2008).

### 2.1.2. Epidemiology and risk factors, screening tools/prevention

Most patients inherit the genetic abnormality from a parent and about 20 to 30% develop the germline abnormality spontaneously (Varesco, 2004). FAP affects both sexes equally (NORD, 2017), and in most cases, FAP is inherited as a highly penetrant trait. FAP has a birth incidence of 1 in 10,000 (Vasen, et al., 2008). According to national registries, FAP occurs in 2.293.2 per 100,000 individuals worldwide (NORD, 2017); it occurs in 5,000 to 10,000 individuals in the United States (US) (Aretz, et al., 2004). FAP accounts for about 0.5% of all colorectal cancer cases (NORD, 2017).

The primary treatment option for the syndrome includes extensive endoscopic monitoring and polypectomy. As standard of care, FAP patients with intact colons undergo serial colonoscopies approximately yearly. As polyposis burden progresses, or adverse histology (high-grade dysplasia, villous adenoma) is identified, colectomy, or proctocolectomy is advised. To prevent colorectal cancer, most patients with FAP undergo prophylactic colectomy in the second or third decade of life; the rectum is retained after ileorectal anastomosis (IRA) but total proctocolectomy with ileal pouch-anal reconstruction (IPAA) may be indicated for those patients with extensive rectal polyps (Vasen, et al., 2008; Kim and Giardiello, 2011). This age range frequently is a transition time for life events, such as completing secondary school, initiating or completing post-secondary education, joining the workforce, and/or getting married. Delaying/preventing colectomy allows for flexibility in timing based on these life events. The management goal is to maintain adequate bowel function (stool frequency, urgency, soilage) and delay or avoid the need for life-altering surgery which may result in a permanent ileostomy. The frequency of endoscopic follow-up of the rectum after IRA varies between 3–6 months; follow-up is indicated after IPAA at intervals of 6–12 months (Vasen, et al., 2008).

After colectomy, patients with a retained rectum or ileal pouch neorectum commonly develop progressive adenomatous neoplasia and are at risk for worsening bowel function and cancer. After their initial colectomy with IRA or proctocolectomy with IPAA, patients undergo regular proctoscopies. An increase in overall rectal/pouch adenoma burden raises cancer risk, and may require proctectomy or pouch resection, both with likely permanent ileostomy. The management goal for these patients is to maintain adequate bowel function (stool frequency, urgency, soilage) and delay or avoid the need for life-altering

permanent ileostomy. By delaying the development of "advanced" or "pre-cancerous" adenoma (≥ 10 mm [1 cm]) and/or high-grade dysplasia or villous histology), serial polypectomies can be minimised (van Stolk, et al., 1998; Martinez, et al., 2001). Such excisional procedures over time produce increased rectal or pouch scarring, which impacts bowel function.

More than 90% of patients with FAP develop duodenal and ampullary adenomas later in life. Surveillance usually requires general anesthesia and may be as frequent as every 6 months. Options for treating FAP patients with duodenal disease can include advanced endoscopic procedures, such as endoscopic mucosal or submucosal resections, or ampullectomy. Duodenal adenomas are often flat, coalescing into large plaques that are difficult to remove. Major surgical interventions, such as duodenectomy or pancreaticoduodenectomy (Whipple procedure), are recommended for FAP patients with cancer on duodenal biopsy and/or progression of disease severity to that which cannot reliably be managed by endoscopy.

### 2.1.3. Biologic features and pathogenesis

The natural polyamines putrescine, spermidine and spermine are intimately involved in growth-related processes, wound healing, and the development of cancer. Under normal conditions, the pool of polyamines is tightly controlled through regulation of synthesis, catabolism and transport mechanisms (Gerner and Meyskens, 2004). The loss of this tight control can result in an excessive accumulation of putrescine and spermidine, which favours malignant transformation of cells. An example of loss control occurs through mutation of the adenomatous polyposis coli (APC) tumour suppressor gene resulting in the development of familial adenomatous polyposis (FAP) (Gerner and Meyskens, 2004).

Mutation of the APC suppressor gene and loss of its protein product causes an elevation in putrescine and spermidine levels, which results in a malignant transformation of colonic mucosal cells and the development of colorectal tumours (Gerner and Meyskens, 2004). The APC gene product normally suppresses the oncogene c-Myc which in turn suppresses ornithine decarboxylase (ODC) activity. The loss of the APC gene product causes c-Myc to enhance the activity of ODC increasing polyamines to abnormal concentrations.

Eflornithine (difluoromethylornithine, DFMO, CPP-1X) is an irreversible inhibitor of ODC (Meyskens and Gerner, 1999). The administration of eflornithine decreases both ODC activity and polyamine concentrations (Gerner and Meyskens, 2004; Gerner and Meyskens, 2009). As soon as the spermidine concentration decreases below a critical level the cells are unable to complete the cell cycle and stop growing. Studies in animal models of FAP indicate that eflornithine alone is effective in reducing the number of intestinal (Erdman, et al., 1999) and colonic (Yerushalmi, et al., 2006) tumours. In genetic mouse models with an APC gene mutation, the administration of eflornithine reduces intestinal carcinogenesis.

ODC enzyme activity and polyamine contents are elevated in the apparently normal colonic mucosa of genotypic FAP patients compared to FAP family members without FAP (Giardiello, et al., 1997). These mechanistic and translational studies in humans indicate that ODC enzyme activity is upregulated in the intestinal and colonic mucosa of patients with FAP.

### 2.1.4. Clinical presentation, diagnosis and prognosis

The standard clinical diagnosis of typical/classical FAP is based on the identification of >100 colorectal adenomatous polyps.

Disease progression in patients with FAP occurs as a continuum across the patient's life span.


**Figure 1: Disease progression in patients with familial adenomatous polyposis**

FAP is characterised by the development of hundreds to thousands of adenomas in the colorectum usually beginning during childhood and in adolescence (Vasen, et al., 2008). Without surgical intervention, there is almost a 100% chance the adenomas will develop into colorectal cancer by the mean age of 40 to 50 years (Vasen, et al., 2008). Later in life, duodenal polyposis develops. The treatment of duodenal adenomas depends on the severity of the disease; if untreated, these progress to malignancy in approximately 5% of cases (Vasen, et al., 2008).

### 2.1.5. Management

Current standard of care for patients with FAP is serial upper and lower GI endoscopies to determine polyposis progression and detect high-risk adenomas and cancer early. The age at which screening should start depends on the risk of malignant transformation of the colorectal adenomas and may begin before the age of 10 in some patients. In symptomatic patients, endoscopic investigation may be indicated at any age (Vasen, et al., 2008). Prophylactic colectomy or proctocolectomy is usually required in the late teenage years or young adulthood and is ideally performed early enough to avoid cancer. The International Society for Gastrointestinal Hereditary Tumours (InSIGHT) 2016 management guidelines indicate that the timing of surgery is at the discretion of the surgeon and patient; however, rectum and colon adenoma burden or the identification of advanced histology in polyps also factor into the decision-making process (Lynch, et al., 2016).

For patients with FAP, initial colon or colorectal surgery is followed by lifetime serial proctoscopy and upper GI endoscopies, with procedures performed as often as every 6 months. Resectional interventions, either advanced endoscopic or surgical procedures, are usually required as adenoma burden continues to increase over time to prevent or treat cancer. In addition to preventing cancer, major objectives of disease management are to minimise/defer the need for life-altering surgeries and maintain bowel quality of life. This is most relevant for the lower intestine (colon, rectum, or ileal pouch). The negative effects on bowel quality of life include the requirement for a temporary or permanent ileostomy, frequent bowel movements (average 6 per day), night-time fecal soilage, and reduced female fecundity. In a study of 525 individuals in 145 families at high risk of FAP, surgically treated patients with FAP reported significantly reduced health-related quality of life compared to those patients who had not yet had surgery (Douma, et al., 2011). Self-report questionnaires assessed generic- and condition-specific health-related quality of life and the consequences of FAP for daily life.

There are no approved pharmacologic treatments for FAP in the US or in Europe. In 2003, celecoxib (Onsenal®) was approved under exceptional circumstances by EMA for the reduction of the number of adenomatous intestinal polyps in FAP, as an adjunct to surgery and further endoscopic surveillance. However, after a decade, the Sponsor voluntarily withdrew the Marketing Authorisation. The reason given was that the MAH was not able to provide the additional data required to fulfil its specific obligation, as a result of slow enrolment in an ongoing efficacy and safety clinical trial.

The role of selective COX-2 inhibitors in patients with FAP is controversial. Celecoxib did not become a usual part of the standard care for patients with FAP due to the risk of serious cardiovascular events.

Pharmacotherapy could benefit patients across the continuum of the disease as an adjunct to endoscopic surveillance. For those patients who have an intact colon, pharmacotherapy offers the opportunity to

control or delay polyposis progression, the decision on timing of colectomy or proctocolectomy by patients in conjunction with their physician to a time that is less personally, socially, and professionally traumatic given the young age of FAP patients confronting this major surgery. For those who have had their initial colon procedure, supplementation of endoscopic surveillance with pharmacotherapy offers the potential to reduce the frequency of lifelong endoscopy (thereby increasing patient adherence to surveillance), reduce the risk of developing advanced pre-cancerous adenomas (≥ 10 mm adenoma, high-grade dysplasia, villous adenoma), and halt or delay the progressive increase in polyp burden. Treatment of these problems has the major potential for improving quality of life by mitigating the need for additional surgical procedures that may ultimately lead to a permanent ileostomy.

## *About the product*

Eflornithine (difluoromethylornithine, DFMO, CPP-1X) is an irreversible inhibitor of ODC.

Sulindac is a member of the arylalkanoic acid class of nonsteroidal anti-inflammatory drugs (NSAIDs) and is a non-selective inhibitor of the cyclooxygenases involved in prostaglandin synthesis.

Studies in animal models of FAP indicate that eflornithine alone is effective in reducing the number of intestinal and colonic tumours (Erdman et al 1999, Yerushalmi et al 2006). Eflornithine works in combination with the nonsteroidal anti-inflammatory drug (NSAID), sulindac, to further reduce tissue polyamine contents, as sulindac activates polyamine export mechanisms.(Babbar et al 2003) Combinations of eflornithine and NSAIDs have been shown to reduce the number of advanced adenomas by more than 90% in mouse models of FAP. (Henkaus et al, 2008) These results provide strong evidence that patients with FAP should respond to this therapy.

The major evidence for benefit of eflornithine derives from prospective, randomised, placebo-controlled clinical studies of eflornithine monotherapy in patients with elevated risk for developing certain forms of cancer (prostate (Simoneau et al 2008) and basal cell skin cancer (Bailey et al 2010)). Clinical studies with eflornithine monotherapy have also been conducted with study endpoints consisting of tissue polyamine contents. These markers are dependent on ODC, the eflornithine target protein. Eflornithine has been shown to reduce rectal mucosal tissue polyamine contents in a randomised, placebo-controlled, clinical study in subjects with a history of resected colon polyps. (Meyskens et al 1998) This marker study is especially relevant to patients with FAP, in whom target tissues include intestinal and colonic mucosa.

Meyskens and colleagues performed a Phase 2/3, double-blind study in which 375 subjects with resected sporadic adenoma were treated for 3 years with eflornithine (500 mg once a day) + sulindac (150 mg once a day) (N=191) or matched placebo/placebo (N=184). Results 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 with the active combination regimen compared to placebo. (Meyskens et al 2008)

Both active substances have been previously approved in the EU in other formulations and for different indications as the one applied in this submission.

Pharmacological classification.

*The proposed pharmacotherapeutic group for Flynpovi is "antineoplastic agents".*

The proposed posology for the treatment of adult patients with familial adenomatous polyposis (FAP) who have an intact colon, rectum, or ileo-anal pouch, as an adjunct to standard of care, is 2 tablets once daily with food at the same time each day.

### *Type of application and aspects on development*

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.

The applicant has stated that the CPP-FAP-310 study has provided an extensive amount of data leading to a better understanding of FAP, its natural history, and key differences between upper and lower GI disease for these patients. It also has shown that the Spigelman Stage Progression, although useful for surveillance cancer risk, is not a valid surrogate for a "need for surgery." Although FAP has proven to be a difficult disease to study, the CPP-FAP-310 trial clearly shows a benefit and potential to significantly delay life-altering surgical events in the lower GI tracts of patients. The ability to delay or prevent colectomy, proctectomy, or pouch resection represents a clear advancement in FAP disease management and a positive benefit/risk balance.

- It is likely that the applicant will be able to provide comprehensive data.

The applicant intends to conduct a follow-up study in adults and adolescents with FAP to demonstrate Flynpovi can effect a reduction in the need for and to delay the time for major surgeries or the development of pre-cancerous adenomas in the lower GI tract compared to sulindac alone, to support a CMA.

- Unmet medical needs will be addressed.

The applicant states that an unmet need exists for patients with FAP. There are currently no available pharmacotherapies for treatment of FAP. In 2003, celecoxib (Onsenal) was approved under exceptional circumstances by EMA for the reduction of the number of adenomatous intestinal polyps in familial adenomatous polyposis (FAP), as an adjunct to surgery and further endoscopic surveillance. However, after a decade, the MAH voluntarily withdrew the Marketing Authorisation due to the inability to provide the additional safety and efficacy data required by the EMA in the initial approval. Current standard of care consists of regular endoscopic monitoring and polypectomy, with most patients undergoing prophylactic colectomy or total proctocolectomy between 15 and 25 years.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

The applicant states that the orally administered pharmacotherapy represents a therapeutic advantage over surgical interventions which impacts quality of life for FAP patients.

## *2.2. Quality aspects*

### 2.2.1. Introduction

The finished product is presented as film coated tablets containing a fixed combination of 288.6 mg eflornithine (as hydrochloride) and 75 mg sulindac as active substances.

The product is available in opaque PVC/PCTFE/PVC-aluminium blister.

## 2.2.2. Active Substance

**Eflornithine hydrochloride**

***General information***

Eflornithine hydrochloride is a well-known active substance. It is not monographed in European Pharmacopoeia or a pharmacopoeia of a member state. The chemical name of eflornithine hydrochloride is 2-(difluoromethyl)-DL-ornithine hydrochloride monohydrate corresponding to the molecular formula $C_6H_{12}F_2N_2O_2.HCl.H_2O$. It has a relative molecular weight of 236.65 and the following structure:

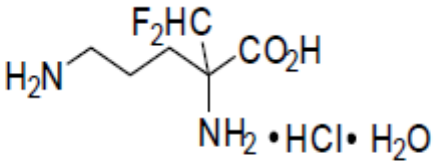



**Figure 2: Eflornithine hydrochloride structure**

The chemical structure of the active substance was elucidated by a combination of elemental analysis, Infrared (IR), mass spectrometry (MS) and nuclear magnetic resonance (NMR).

The active substance is a non-hygroscopic white to off-white powder  freely soluble in water; soluble in methanol; sparing soluble in ethanol; very slightly soluble in hexane; insoluble in chloroform and toluene.

Eflornithine hydrochloride exhibits stereoisomerism due to the presence of one chiral centre and exists as a racemic mixture that contain equal quantities of enantiomers, D form and L form.

Polymorphism has been observed for the active substance. There are three solid forms described. The active substance was characterised by X-Ray Powder Diffractometer (XRPD) and a consistent solid form (Type 3) is obtained through manufacturing process.

***Manufacture, characterisation and process controls***

An Active Substance Master File (ASMF) procedure has been followed to provide information on the active substance. The active substance is manufactured by two manufacturing sites.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Eflornithine hydrochloride is synthesised by a process from well defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is double packed in low density polyethylene (LDPE) bag/tubing which complies with the EC directive 2002/72/EC and EC 10/2011 as amended. The package bag/tubing are sealed with twist ties under nitrogen. Structural support is provided by high density polyethylene (HDPE) drum/bottle that do not contact the product.

***Specification***

The active substance specification includes tests for appearance (visual), identification (IR, HPLC), water content (Ph. Eur.), residue for ignition (Ph. Eur.), impurities (Ph. Eur.), residual solvents (Ph. Eur.), assay (Ph. Eur.) and particle size (Ph. Eur.)

The impurities are classified and specified according to relevant EMA and ICH guidelines. Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The acceptance limits for residual solvents are justified according to ICH Q3C.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used has been presented.

Batch analysis data from 15 pilot and commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

***Stability***

Stability data from 6 commercial scale batches of the active substance from the proposed manufacturer stored in the intended commercial packagefor up to 60 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: appearance, water, assay, impurities, color of solution, and microbial enumeration test.

No obvious degradation is observed from the current stability data for the first manufacturing site. Results indicated that the active substance is chemically stable at above conditions after storage for 60 months.

Photostability testing following the ICH guideline Q1B was performed on 4 batches. The result indicated that eflornithine HCl is physically and chemically stable when exposed to the lighting.

Four batches were placed in an oven at 60°C and subsequently assayed at 1 and 2 months. The temperature was then raised to 85°C and the samples re assayed after 2.5 months at these conditions. Once again, the temperature was raised to 150°C and the samples were allowed to remain in the oven for an additional 2 months, at the end of which they were re assayed and the study terminated. The total time from the beginning of the study to the end was, therefore, 6.5 months. The results indicate that eflornithine hydrochloride is highly stable, even under conditions of extreme heat.

The storage condition is proposed in order to have better control on the active substance despite the fact that eflornithine HCl is stable when exposed to moisture, heat, and light according to hygroscopicity study and forced degradation study, respectively.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period and storage conditions.

**Sulindac**

***General information***

Sulindac is a well-known active substance monographed in European Pharmacopoeia. The chemical name of sulindac is (Z)-[5-Fluoro-2-methyl-1-[4-(methylsulfinyl)benzylidene]-1H-inden-3-yl]acetic acid or [(1Z)-6-Fluoro-3-[[4-[(RS)-methanesulfinyl]phenyl]methylidene]-2-methyl-3Hinden-1-yl]acetic acid corresponding to the molecular formula $C_20H_{17}FO_3S$. It has a relative molecular mass of 356.4 g/mol and the following structure:

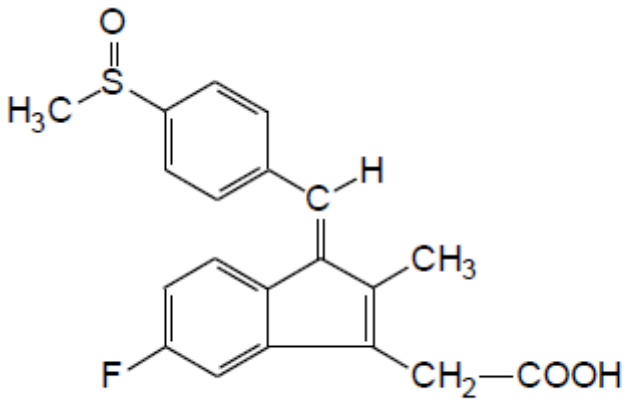



**Figure 3: Sulindac structure**

The chemical structure of sulindac was elucidated by a combination of UV spectrum, IR spectrum, nuclear magnetic resonance ($^1$H NMR), and mass spectrum (MS). The solid-state properties of the active substance were measured by X-ray powder diffraction (XRDP) and the infrared absorption.

Suindac is a non-hygroscopic yellow crystalline powder slightly soluble in methanol, in ethanol, in acetone, and in chloroform; very slightly soluble in isopropanol and in ethyl acetate; practically insoluble in hexane and in water.

The presence of a double bond between C and the indene ring gives rise the possibility of two isomeric forms: cis (named also Z) and trans (named also E). The synthetic process employed produces sulindac having configuration Z. The presence of the E-isomer in the product is routinely determined by HPLC in the specifications.

Polymorphism has been observed for sulindac. Sulindac can exist in two non-solvated enantiotropic crystal forms designated Forms I and II. The X-ray powder diffraction and the infrared absorption can distinguish the two forms. Sulindac is produced routinely as Form II.

***Manufacture, characterisation and process controls***

An Active Substance Master File (ASMF) procedure has been followed to provide information on the active substance.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it is considered satisfactory.

Sulindac is synthesised in 2 main steps using commercially available well-defined starting material with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

The specified related substances of sulindac are described in the Ph. Eur. Monograph.

The active substance is packaged in polyethylene bag, into a drum lined with a second food grade polyethylene bag which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

***Specification***

The active substance specification complies with the Ph. Eur. monograph includes tests for appearance (visual examination), identification (IR), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), related substances (HPLC), assay (potentiometric titration), and related solvents (HS-GC).

The specification currently set for sulindac is compliant to the new current Ph. Eur. Monograph for sulindac. The specification limits for related substances are aligned with the current official Ph. Eur. monographs.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used has been presented.

Batch analysis data on 3 batch commercial batch size of the active substance are provided. The results are within the specifications and consistent from batch to batch.

***Stability***

Stability data from 3 commercial scale batches of active substance from the proposed manufacturer stored simulating that used for marketing for up to 60 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: appearance, loss on drying, chromatographic purity, related purity and assay. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of any particular storage condition in the proposed container.

## 2.2.3. Finished Medicinal Product

***Description of the product and Pharmaceutical development***

The finished product (FP) is a combination product with eflornithine HCl and sulindac as active substances. The combination product is an immediate release drug formulation for oral administration supplied as a yellow, oblong, scored tablet engraved with "1X" and "S" on one side with the following dimensions: approximately L 17.2 mm x w 5.7 mm

Concern regarding patient compliance and the desire to make the treatment regimen easier for the patients led to the development of a co-formulated tablet containing both eflornithine and sulindac, whereby only two identical tablets would be taken daily. The development goal was to realise a tablet containing 346.5 mg of anhydrous eflornithine HCl as eflornithine hydrochloride monohydrate (375 mg) and 75mg of sulindac in as small a tablet.

Eflornithine hydrochloride monohydrate is freely soluble in water and exhibits different crystalline forms depending on the crystallisation solvents. All the crystalline forms are freely soluble in water. It has been demonstrated that one crystalline form is produced. Sulindac is practically insoluble in water. A separate solubility study at different pH shows that sulindac is slightly soluble in physiological range. Sulindac is a polymorphic substance and can exist in two non-solvated enantiotropic crystal forms designated as form I and form II.

Specific excipients have been used which have been chosen concerning the following factors: equivalent to comparable products, compatibility with the active substances, and compatibility with oral administration. A detail active substance-excipient compatibility study with potential excipients was conducted and revealed that the potential excipients are compatible with both eflornithine HCl and sulindac. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation.

The scored tablet design was initially adapted in anticipation of future need in paediatric population. Based on the clinical studies completed, dosing does not require use of half tablet. However, the scored tablet design has been maintained throughout development, clinical batch production and scale-up studies and is proposed for commercialisation. Characterisation data as per the relevant guidelines was collected during development to support scored tablet. Since the current clinical plan no longer requires use of half tablet dosing, information and data supporting use of whole tablet has been presented in the submission.

One pilot-scale batch was manufactured to compare pharmacokinetic parameters of eflornithine, sulindac, sulindac sulfide and sulindac sulfone in plasma following oral administration of a co-formulated tablet versus individual tablets. This same batch has also been put on stability studies.

Further development studies were performed after the manufacture of pilot bioequivalence (BE) batch for the improvement of the film coating, the dissolution profile and optimisation of the manufacturing process. The resulting formulation was used in the manufacture of 3 registration batches. The three batches resulted compliant to the finished product specifications and were manufactured according to parameters defined in the protocol and its amendments.

A forced degradation study was performed with the purpose of establishing the degradation pathways of the two active substances, eflornithine HCl monohydrate and sulindac, as a combination or as single entities, and to verify that the analytical procedures are appropriate for the determination of the assay and the main degradation products. A single batch of the finished product, the placebo tablets and each active substance as a single entity or in combination were exposed to this study. The selected degradation conditions were acid/basic hydrolysis, oxidation, light, heat, heat and humidity. The finished product was stable at temperature and light exposure. In the finished product, both substances showed no significant degradation and alteration of their structure after temperature or light exposure. The mixture of both substances did not stimulate the generation of degradation products, whatever the degradation conditions applied, and no degradation products are detected at wavelengths other than the one for the analytical procedures. It was reported that the mass balance for both substances is globally respected; moreover, the selection of the HPLC method as an indicative and satisfactory method for the detection of both active substances in the finished product was justified.

The robustness of the formula and the process have been assessed at laboratory and pilot scale, applying a quality by design (QbD) methodology. However, no design space has been claimed. The following parameters have been studied as part of the risk assessment matrix within the tooling screening study: the influence of tooling design with regards to appearance and breakability, half tablet content uniformity and half tablet dissolution. Two sets of tooling were used in these studies: tooling A for tablet dimensions of 17 mm x 7 mm and tooling B for tablet dimensions of 17 mm x 7.5 mm. The influence of tooling design on tablet quality attributes was studied at the compression step and after the film-coating step. Since almost no influence on tablet characteristics was observed from the compression force parameters, compression force ranges supporting compliance with breakability and appearance specifications were confirmed as. Additionally, the tablets were film-coated and tested to assess breakability by half tablet mass, dissolution, and half-tablet content uniformity. Since the robustness of the compression process for tooling B was significantly better, this tooling set was used in the subsequent design of experiment (DoE) trials. As part of the DoE trials, the physical quality of eflornithine, the impact of the source of magnesium stearate, the mixing duration, the compression and coating parameters were assessed. Visually no impact of parameters on physical and analytical attributes of tablets have been detected.

Bioequivalence study was performed showing bioequivalence between the clinical formulation and the proposed commercial formulation.

No comparative dissolution profiles of batches used in bioequivalence studies were provided. A dissolution profile for the bio-batch with the final dissolution method was provided. However, the tested tablets were uncoated.

In relation to the manufacturing process development, the robustness of the formula and the process has been assessed at laboratory and pilot scale and scalability was verified. A second risk assessment has been performed after manufacture of the technical scale up batch and prior to manufacture of the primary stability batches/bioequivalence batch, finding acceptable ranges to be applied in the process at industrial scale for the steps mixing 2, compression and film-coating. During the development the manufacturing process was simplified.

The primary packaging is PVC/PCTFE/PVC-aluminium blister. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

### *Manufacture of the product and process controls*

The finished product is manufactured by one manufacturing site

The manufacture of the combination product is considered to be a standard manufacturing process. Accordingly, the process will be validated with full commercial size batches prior to commercialisation. This is considered satisfactory. A process validation protocol has been provided. The in-process controls are adequate for this type of manufacturing process.

### *Product specification*

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance and color (visual), identification of active substances (HPLC, IR), uniformity of dosage by content uniformity (Ph. Eur.), dissolution of active substances (Ph. Eur.), assay of active substances (Ph. Eur.), degradation products (HPLC), microbiological quality (Ph. Eur.).

Sulindac impurities are specified as for the active substance itself and specification are as per compendial limits. Eflornithine lactam and each unspecified degradation product is established per ICH Q3B guideline based on the total daily dose of finished product.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 3 batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020) was requested by CHMP. This question was raised as a Major Objection. Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used has been presented.

Batch analysis results are provided for 3 pilot and 1 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing

***Stability of the product***

Stability data from 3 pilot scale batches of finished product stored for up to 24 months under long term conditions (25ºC / 60% RH),for up 24 months under intermediate conditions (30°C / 65% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No change was noticed on the finished product.

Based on available stability data, the proposed shelf-life without any special storage conditions is acceptable.

***Adventitious agents***

No excipients derived from animal or human origin have been used.

## 2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and

uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the assessment of this application, there were a number of major objections (MOs) raised by the CHMP. All these issues were satisfactory resolved during the procedure by the submission of additional information and data by the applicant.

The applicant has applied QbD principles in the development of the finished product and its manufacturing process. However, no design space was claimed for the manufacturing process of the finished product.

### 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues which might have negative impact on the benefit/risk balance.

### 2.2.6. Recommendation(s) for future quality development

Not applicable.

## *2.3. Non-clinical aspects*

### 2.3.1. Introduction

This application includes a limited number of sponsor-conducted studies, together with data from the published literature. Both active substances have been previously approved in the EU in other formulations and for different indications. For eflornithine, the applicant conducted an *in vitro* hERG assay and a pharmacokinetics (PK) study evaluating effects on CYP450 and drug transporters. Safety pharmacology, PK, toxicology, reproductive and developmental toxicity and genotoxicity studies conducted for an iv eflornithine product Ornidyl (authorised in the US, NDA #019878) are also included, for which the applicant, CPP, has a right of reference. Also, pharmacodynamics (PD), PK, toxicology, developmental and reproductive toxicology, carcinogenicity, genotoxicity and other toxicity studies from the published literature are referenced. For sulindac, the applicant conducted an *in vitro* hERG assay and includes data from the published literature on PD, PK, toxicology, developmental and reproductive toxicology and carcinogenicity. In addition to the non-clinical data that CPP as the applicant relies upon for this application, information was presented in the dossier from the Summary Basis of Approval for Clinoril (FDA, 1978), the Product Monograph for Sulindac Tablets, USP (TEVA, 2011), and the Investigator's Brochure from Marion Merrell Dow (Marion-Merrell Dow, 1987) as supportive information only.

### 2.3.2. Pharmacology

In patients with hereditary FAP, enzyme activity of ornithine decarboxylase (ODC) is increased. ODC is the first enzyme in the pathway for polyamine biosynthesis and catalyses the conversion of ornithine to putrescine and regulates the biosynthesis of polyamines in mammalian as well as many other eukaryotic cells. Because of increased ODC levels, polyamine concentrations are elevated in the intestinal and colonic mucosa of patients with FAP. A specific association between the increase in polyamine synthesis and some primary and/or secondary events involved in eukaryotic cellular growth and differentiation has

been identified. In particular, increased polyamine concentrations have been associated with cell transformation, induced carcinogenesis, and tumour cell proliferation.

## *Primary pharmacodynamic studies*

Eflornithine is an antiproliferative agent which inhibits the enzyme ODC. Sulindac is a NSAID that exhibits anti-inflammatory, analgesic and antipyretic activities and inhibits the platelets function.

A summary of the publicly available literature was presented in this application on the effects of eflornithine and sulindac alone and in combination in *in vitro* and *in vivo* models of carcinogenesis. Eflornithine is reported as being an irreversible inhibitor of ODC resulting in decreased ODC activity, decreased intracellular concentrations of polyamines putrescine and spermidine and decreased cell growth in *in vitro* hepatoma and colon adenocarcinoma cell lines. Sulindac and metabolite sulindac sulfone are reported as producing anti-proliferative effects *in vitro* in human adenocarcinoma cells and Caco-2 human adenocarcinoma cells respectively. The *in vitro* dissociation constant (KD) for racemic eflornithine at ODC has been reported as 2.2 µM. Sulindac has an $IC_{50}$ value of 13.85 µM and 196 µM against COX1 and COX2, respectively. Sulindac sulfide demonstrates higher potency with $IC_{50}$ values of 0.017 µM and 0.55 µM against COX1 and COX2, respectively.

The effects of eflornithine administration via drinking water on GI polyamine concentrations and tumour incidence have been assessed in multiple intestinal neoplasia (Min) mice heterozygous for the APC allele and in rodent models of colorectal cancer following carcinogen administration. The results of the submitted studies are model dependent. Eflornithine is reported to reduce small intestinal tumour incidence and polyamine levels, but not colon polyamines or tumour incidence in the Min mouse model. Following supplementation with ODC substrate arginine, eflornithine administration was associated with no difference in small intestinal tumour burden but was associated with an attenuation in arginine induced increase in colonic tumourigenesis. The authors conclude that this may indicate a protective role for eflornithine in colon tumourigenesis specifically induced by dietary factors. Studies assessing colonic tumour incidence following the administration of carcinogen DMH to mice (Kingsnorth et al. 1983; Tempero et al. 1989) report a reduction in tumour incidence following eflornithine administration following DMH administration, but also reports that co-administration of eflornithine only during the period of DMH treatment was not protective i.e. continued administration post exposure is necessary for significant attenuation of tumour induction. Eflornithine was reported as dose dependently reducing the frequency of azoxymethane (AOM) induced tumours in both the small and large intestine in a rodent model. This effect correlated with a reduction in ODC activity.

The applicant has submitted a summary of studies reporting that oral sulindac administration decreases tumorigenesis in the $Apc^{Min/+}$ mouse model (Beazer-Barclay et al. 1996; Boolbol et al. 1996). Data from this model suggest that continuous administration is required to maintain this protective effect. A study examining the effect of direct administration of the sulfone and sulphide metabolites in this model suggests this effect is primarily related to the sulfone metabolite (Mahmoud et al. 1998). Of note, in one study (Yang et al, 2003), while administration of sulindac in diet or water was associated with a decreased total intestine and specifically small intestine tumour incidence, it was associated with an increase in colon tumour incidence, multiplicity and volume. The applicant has provided summaries of two other studies examining sulindac activity utilising a different rat model, the PIRC (Polyposis in the Rat Colon) (F344/NTac-Apc am1137), which as it spontaneously develops colon tumours has been suggested as a better model for colon carcinogenesis in FAP. In one such study (Femia et al., 2015), PIRC rats treated with sulindac at a dose of 320 ppm daily in diet exhibited a significant decrease in mucin depleted foci (these have previously been correlated with carcinogenesis) in the colon. A second study by Femia and Colleagues (2015) aimed to assess the effect of 80 and 320 ppm sulindac in diet following long term treatment to PIRC rats, specifically in response to the findings of Yang et al., (2003) in Apc mice.

They found that sulindac administration at 320 ppm was associated with a significant decrease in colon tumours relative to control in the PIRC rat. Both doses were associated with a statistically significant decrease in total tumours with an apparent mild dose response relationship. Of note, though both doses were associated with a numerical decrease in small intestine tumours relative to control, these were not statistically significant.

The potential safety implications of the findings of increased colon tumours in ApcMin/+ mice following sulindac administration in the Yang et al (2003) study, have not been addressed by the applicant, however additional data submitted suggest model specific differences in the sulindac chemoprotective activity. It is accepted that as these are academic PD studies and no direct clinical relevance can be inferred.

Studies in murine models of carcinogen induced colorectal cancer suggest that sulindac treatment is protective for DMH induced tumourigenesis but did not decrease tumour burden once administered 10 days following DMH administration (Moorghen et al. 1998). Further studies in rodent models report that although sulindac was not associated with a reduction in established tumour burden, treatment did result in a reduction in the rate of DMH-induced tumour growth (Skinner, Penney, and O'Brien 1991). Another study examining a different treatment protocol in a rat AOM induced colon carcinogenesis model reported that treatment with sulindac 14 weeks following AOM administration produced better protective effects on colon tumour incidence than animals treated during AOM administration (Rao et al. 1995).

A single *in vivo* study examining the effects of sulindac and eflornithine together in the $Apc^{Min/+}$ mouse model (Ignatenko et al., 2008) has been submitted. The authors of this paper state that the combination performed better in terms of a decrease in 'high grade adenomas', but this was only statistically significant when presented in terms of percentage of total adenomas/group, not when assessed in terms of absolute numbers/mouse. This is considered a confounded variable due to the low total incidence of tumours/mouse in several of the treated groups and presenting the data this way is considered misleading. Only the combination of sulindac and eflornithine produced a statistically significant decrease in total polyamine levels in the small intestine in this study. Of note, in this study, sulindac alone (167 ppm in diet) produced the numerically greatest reduction in tumour number/animal but was also associated with the highest total polyamine levels. No correlation between small intestine total polyamine levels and tumour or high grade adenoma incidence were evident, but it should be noted the polyamine levels in this study were highly variable.

### *Secondary pharmacodynamic studies*

The applicant has provided information on secondary pharmacological targets of both mono-components sourced from the publicly available literature. In addition to the primary PD activity at COX1 and COX2, sulindac, sulindac sulfide, and sulindac sulfone have also been reported to act via the NF-kB pathway. Sulindac metabolite, sulindac sulphide has also been reported to inhibit PDE5, which may be related to its purported anti-tumorigenesis activity. Eflornithine is reported as an inhibitor of L-arginase.

### *Safety pharmacology programme*

The applicant has submitted GLP-compliant *in vitro* studies assessing the effects of eflornithine and sulindac (individually) on hERG channels expressed in HEK cells. For eflornithine, the $IC_{50}$ value for the hERG channel in these experiments was estimated as greater than 10000 µM. For sulindac, the $IC_{50}$ value for the hERG channel in these experiments was 294.4 µM. This represents a significant margin to anticipated sulindac Cmax (≈ 7 µM based on study CPP-P6-366).

No dedicated *in vivo* safety pharmacology studies have been performed. ECG effects associated with eflornithine administration were assessed as part of a two week repeat-dose toxicity study conducted in dog at doses of up to 1000 mg/kg/day (T-81-34). Although this study is stated as being performed to GLP, it was completed in 1981 and it is not clear what the differences to modern GLP may have been. No change is reported in ECG measures in this study, however, this appears to have been only a qualitative comparison, with no quantitative data presented. Furthermore, no TK data are presented. No relevant data on respiratory safety pharmacology have been presented.

No *in vivo* safety pharmacology studies for sulindac have been submitted. Reference is made to the US label for sulindac containing medicinal product Clinoril. The submitted safety pharmacology data and discussion are not considered sufficient to meet the minimum criteria as outlined in ICH S7A and B. Following a request for additional data, the applicant has submitted additional discussion on the non-clinical data CV safety pharmacology (GLP-compliant in-vitro hERG assays for both mono-components, and GLP-compliant 14-day dog repeat-dose toxicity study which included a qualitative assessment of ECGs) as well as a summary of the available clinical data related to cardiovascular for risk for each mono-component and for the combination. Although the available data do not currently meet the minimum requirements for safety pharmacology data as outlined by ICH M7, in view of the available clinical data, additional in-vivo NC safety pharmacology data may not be relevant. The limitation of the *in vivo* safety pharmacology data has been reflected in section 5.3 of the SmPC.

### *Pharmacodynamic drug interactions*

No new non-clinical studies were conducted to assess potential pharmacodynamics drug interactions.

## 2.3.3. Pharmacokinetics

No new animal studies have been conducted with either sulindac or eflornithine for this application. The applicant has submitted a summary of absorption characteristics of each mono-component based on information sourced from the publicly available literature and for ornithine only, on historic study reports originally conducted in support of the development of Ornidyl, an IV preparation of ornithine licenced in the US.

No dedicated method validation reports have been submitted for the HPLC/fluorescence detection method used for the calculation of toxicokinetic (TK) data in study 228 (13-week tox study in female rats in combination with tamoxifen) and 229 (13-week tox study in female dogs in combination with tamoxifen).

The study report contains an analytical chemistry report in appendix A, which contains data on standard purity and linearity, but no data on analyte stability in rat plasma, matrix effects, intra and inter run accuracy and precision are included.

For studies B27-TXR-1 and B27-TXD-2 (13-Week Oral Toxicity Study of H-(4--Hydroxyphenyl) Retinamide with Oltipraz or Difluoromethylornithine (DFMO) in rats and Dogs respectively), appendix A and B respectively of the submitted study reports contain method validation data for the HPLC/fluorescence detection method used for the analysis of TK. However, validation data presented are handwritten and difficult to interpret.

For studies M067-TXR-1 and M068-95 (13 week subchronic toxicity investigation of oltipraz in combination with DFMO administered by gavage to male and female rats and dogs respectively) information on the analytical chemistry validation is included in appendix B. No formal method validation is included in this report.

Additional discussion on the methods used in each pivotal study was provided by the applicant during the procedure. In general, these include an assessment of linearity and the range of standards used. Although the submitted information related to the methods used appear reasonable, it is concluded that the methods in these studies were not validated to the standard of current guidance (i.e. EMAs 'Guideline on bioanalytical method validation' -EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**). As it is not possible for the applicant to provide any further information or reassurance on this point, this issue is considered resolved. The potential limitations in the analytical methods used should be taken into consideration when considering exposure margins.

Drug plasma concentration data acquired in these studies is limited to a single time point of sampling. Due to the lack of adequate sampling, derivation of TK parameters such as AUC, t1/2, Cmax and Tmax are not possible. Although these data demonstrate exposure to the test article, the lack of appropriate sampling intervals and hence the inability to establish exposure comparisons in terms of AUC is not in line with the ICH S3A "Note for Guidance on Toxicokinetics: A guidance for assessing systemic exposure in toxicity studies" and no justification for this approach has been presented. However, it is not considered that requesting the generation of new TK data at this stage is appropriate or likely to provide relevant data. Based on these limitations, relevant direct exposure comparisons from clinical exposures to those at NOAELs are not possible.

As there are no non-clinical data available comparing absorption following co-administration and mono-component administration, it is not possible to assess the potential for altered absorption of mono-components following FDC administration. It is acknowledged that the potential for altered absorption following co-administration has been assessed clinically in pivotal study 310. As most studies only used either a single or high and low dose of the mono-components it is not possible to comment on dose exposure relationships, though exposures are reported as increasing in a linear manner following single doses in the range of 200 to 2000 mg/kg i.p.

No data related to absorption of sulindac in non-clinical species has been submitted.

The applicant comments that the distribution of eflornithine has been studied in mouse rat and dog. However, only data from mouse sourced from publicly available literature is summarised. Published literature reports highest concentrations in elimination pathways (intestine, liver, and kidney) following 14 hours exposure as part of drinking water. Data from the submitted studies conducted in rats and dogs suggests low plasma protein binding. Given the clinical experience with eflornithine, specifically with topical preparations, the lack of data on melanin binding and phototoxicity assessment is considered acceptable. Sulindac in contrast is reported as highly plasma protein bound. Additional data in a submitted supporting publication indicates that the placenta is freely permeable to sulindac. Although the

submitted non-clinical distribution data is limited it is not considered that requesting additional data will alter the B/R of the product at this time and therefore the provided data is considered acceptable.

The applicant has submitted a summary of results of an *in vitro* study in which eflornithine was incubated with human hepatocytes (study CP101-004). This summary indicates that eflornithine does not undergo significant hepatic metabolism. The potential for induction/inhibition of CYP450 and UGT enzymes was assessed *in vitro* in human hepatocytes and human liver microsomes respectively. No additional information on eflornithine metabolism/metabolites has been presented.

The proposed scheme for sulindac metabolism is presented in the submitted PK summary document. Sulindac sulphoxide is metabolised in the body by reduction to sulindac sulphide, this process is reversible. There is reportedly a low degree of CYP450 involvement in the reduction of the sulphoxide. Sulindac undergoes irreversible oxidation to the 'inactive' sulphone metabolite, which is subsequently conjugated as an ester glucuronide and eliminated.

Eflornithine is reported as rapidly excreted following i.p. administration to mice with a serum t1/2 of 14 minutes. Elimination is also reported as relatively rapid following oral administration to mice in drinking water. In humans 86 % of eflornithine is reported as being excreted unchanged in the urine. Sulindac metabolites and conjugates are also reported as being excreted primarily via urine.

The applicant has presented a summary and study reports for a number of *in vitro* studies examining eflornithine's potential for induction of CYP450 and UGT enzymes in human hepatocytes and inhibition in pooled human liver microsomes and on selected transporters. Eflornithine is reported not to be a direct or time dependent inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5 at concentrations of up to 5.5 mM in human liver microsomes in-vitro (749N-1602). Co-incubation of eflornithine with human hepatocytes at concentrations up to 5.5 mM did not result in significant induction of CYP1A2, CYP2B6, CYP3A4, UGT1A1, UGT1A3, UGT1A9, or UGT2B7 mRNA synthesis (749N-1603). No significant eflornithine induced inhibition of human OATP1B1, OATP1B3, BCRP and P-gp mediated transport and concentrations up to 10 mM and of OAT1, OAT3, OCT1, OCT2, MATE1, and BSEP mediated transport at concentrations up to 3 mM was reported (OPT-2017-159). The IC50 for MATE2-K was 1.52 mM. While this IC50 (no Ki has been calculated) is approximately 38 fold above the Cmax of 40 µM observed in study CPP-366, it is less than the 50 fold outlined in the relevant guidance (CPMP/EWP/560/95/Rev. 1 Corr. 2**). The applicant has submitted a further study examining the effect of eflornithine at concentrations up to 3 mM on metformin basolateral to apical efflux in MDCK-II cells transfected to express OCT2/MATE2-K (OPT-2018-012). The IC50 in these experiments was > than 3 mM. Based on the totality of the data presented it is accepted that inhibition of MATE2-K by eflornithine is unlikely to result in DDI at clinically relevant concentrations. Further studies investigating eflornithine transport in MDCK-II cells or Sd9 insect cell vesicles expressing a number of human transporters demonstrate that eflornithine does not appear to be a substrate for OAT1, OAT3, OCT1, OCT2, MATE1, MATE2-K, BCRP, P-gp or BSEP transporters (OPT-2017-160).

No new data on the assessment of potential for DDI with sulindac has been submitted. Sulindac is not a substrate for P-glycoprotein, and the cytochrome P-450 isoforms 3A4, 2C9, 2D6, 2C19, and 3A4. It is a known inhibitor for cytochrome P-450 1A1 and 1A2, MRP-2, MRP-4, OAT-1 and OAT-3. Inhibition of NTCP, OATP, Bsep, and Bcrp by sulindac, sulindac sulphide, and sulindac sulfone has been reported.

## 2.3.4. Toxicology

Non-clinical toxicology data for the mono-components eflornithine and sulindac, from studies that the applicant CPP has right of reference and the published literature have been submitted to support this application.

## *Single dose toxicity*

The single dose toxicity data consists of eflornithine data from a 1987 Investigators brochure (IB) for an IV product, Ornidyl (Eflornithine Hydrochloride) from Merrell Dow and a Product Monograph for Sulindac Tablets, USP (TEVA, 2011) as supportive information. No acute toxicity study data is available for sulindac.

The study reports for eflornithine single dose toxicity studies, T-84-24 and T-81-17 are also available including statements indicating GLP compliance dated from 1981 and 1984 respectively.

Study T-81-17 includes IV $LD_{50}$ data from eflornithine administration to mice and rats, of 1035 mg/kg and 2134 mg/kg respectively.

Study T-84-24 includes an IV irritation study in monkeys and dogs, indicating that 250mg/kg administered iv 4 times a day (100mg/kg total dose) was tolerated in dogs and monkeys, with emesis reported in dogs. An eflornithine oral $LD_{50}$ of 5000mg/kg is reported in mice and rats, but the supporting study reports are not provided.

The sulindac product monograph (TEVA, 2011) reports a sulindac oral LD50 in mice and rats of 450 and 225 mg/kg, respectively. Toxic effects observed in mice and rats included apathy, ptosis, depression, piloerection, urinary stain and rapid respiration. Severe growth suppression was noted in animals at all dose levels. Gross necropsy findings in the mice that died were slight haemorrhaging of the GI tract, slightly congested lungs, and stomach wall distended with yellowish fluid and slightly congested adrenals. Gross necropsy findings in the rats which died included external evidence of urinary stain and occasional blood stains around the mouth and eye. Internal evidence of gastritis, enteritis, congestion of the lungs and of the adrenal glands was observed.

In summary, the acute toxicity studies in rodents showed that the main effects for eflornithine by IV route were convulsions as well as squealings and depression, whereas the effects for sulindac by oral route were gastritis (haemorrhage), enteritis, congestion of the lungs and of the adrenal glands. No studies were performed with the Eflornithine / Sulindac combination.

## *Repeat dose toxicity*

Eflornithine studies: The applicant has submitted study reports for three 13-week rat studies (B27-txr-1, 228, M067-95). These sub-chronic studies which were sponsored by the National Cancer Institute (NCI) Division of Cancer Protection (DCP), are dated 1994 – 1997. The study reports include statements of compliance with FDA GLP regulations, with the exception of non-GLP validation methods for the analysis of plasma drug concentrations of difluoromethylornithine (DFMO) in study B27-txr-1, and slight degradation of DFMO occurring under storage conditions (purity decreased from 97.03% to 93.13% during the course of the in-life phase of the study) was noted in study 228. These GLP compliance statements for the sub-chronic repeat-dose rat studies cannot be taken as GLP compliant according to current OECD standards but this is not thought to have impacted on the integrity of study interpretation.

Study B27-txr-1 is a 13-week oral combination toxicology study with DFMO, N-(4-Hydroxyphenyl) Retinamide and Oltipraz, which includes 2 DFMO alone groups, 50 mg/kg/day and 500mg/kg/day. Study M067-95 is a 13-week oral combination toxicology study with DFMO and oltipraz in rats, which includes one DFMO alone group (700mg/kg/day). Study 228 is a 13-week oral combination toxicology study with DFMO and tamoxifen, which also includes one DFMO alone group (1000mg/kg/day). From these 3 studies, no effects are reported following administration of 50mg/kg/day eflornithine, with plasma drug concentrations of 6.40 µg/mL and 5.57 µg/mL reported in males and females respectively, 3hr post-dose at week 14. A significant reduction in food consumption and a slight decrease in body weight when compared with the control group is reported at 500mg/kg/day, with plasma drug concentrations of 71.4

µg/mL and 52.1 µg/mL reported in males and females respectively, 3hr post-dose at week 14. However, at 700mg/kg/day no significant changes in body weight and food consumption were observed in study M067-95, which is inconsistent with the findings at 500mg/kg/day study B27-txr-1. Plasma drug concentrations of 32 µg/mL and 80µg/mL are reported in males and females respectively, 1 hr post-dose at week 13 in this study. Also no clinical toxicities were reported at 700mg/kg/day, although 1 male rat died but this was not considered treatment-related. At 1000mg/kg/day in study 228, dermal lesions are reported, primarily occurring around the corners of the mouth, chin, front legs and feet. Decreased body weight was noted, which was likely related to decreased food consumption. Intestinal lesions that were minimal in severity were observed; sternal and femoral bone marrow hyperplasia was observed in half of the animals. Serum albumin, total protein, cholesterol and triglyceride levels were decreased. An increase in white blood cells, and a slight anaemic response is also reported and spleen weights were increased. A plasma drug level of 110µg/ml is reported in female rats, 4 hours post-dose at week 13 in this study. However, the inconsistency between the studies with regard to plasma sampling and the lack of adequate toxicokinetic data with respect to AUC and Cmax, make comparisons between studies impractical and exposure assessments impossible.

In dogs, the sponsor has submitted a study report for a 2-week intravenous repeat-dose study in dogs (T-81-34). It includes a statement indicating GLP compliance, dated 1981. This is not considered indicative of compliance with current OECD GLP regulations. Dogs were administered a total 300 or 1000mg/kg/day iv, divided into 4 daily doses. These dose levels were terminated early due to toxicity emesis, diarrhoea, anorexia, weight loss and death in association with bone marrow hypoplasia. Villous atrophy of the intestinal mucosa was also reported at 1000 mg/kg/day. An 80 mg/kg/day dose level was added, with only infrequent and mild signs (occasional loose stools) reported. No toxicokinetics are included in this study and therefore the exposure associated with the toxicities reported in this study is unknown.

Study reports for three, 13-week repeat-dose toxicity studies in dogs have also been submitted (B27-txd-2, 229, M068-95). Similar to the rat 13-week studies, these study reports include statements of compliance with FDA GLP regulations. These GLP compliance statements are not considered GLP compliant according to current OECD standards but this is not thought to have impacted on the integrity of study interpretation. Study B27-txr-2 is a 13-week oral combination toxicology study with DFMO, N-(4-Hydroxyphenyl) Retinamide and Oltipraz, which includes 2 DFMO alone groups, 25 mg/kg/day and 100 mg/kg/day. Study M068-95 is a 13-week oral combination toxicology study with DFMO and oltipraz in dogs, which includes one DFMO alone group (100 mg/kg/day). Study 229 is a 13-week oral combination toxicology study with DFMO and tamoxifen, which also includes one DFMO alone group (100mg/kg/day). From these 3 studies, a NOAEL was not defined. Dogs receiving 25 mg eflornithine/kg/day had coloured faeces, conjunctivitis, periorbital alopecia and intestinal cysts and the males had testicular and prostatic atrophy and hypospermia. At the 100 mg/kg/day dose, animals exhibited diarrhoea, eye discharge, red ears, alopecia, intestinal cysts and skin inflammation (B27-txr-2). In study 229, at 100 mg/kg/day body weights were slightly but not significantly lower than control values. Vaginal discharge was observed in one dog and excess eye secretion and salivation and vomiting was periodically observed. Reticulocyte counts were decreased at Week 4. Cornified epithelium of the vagina and cervix was noted in 1/4 and 2/4 dogs, respectively; ovaries were atrophied and crypt microabscesses of the GI tract were observed in 4/4 animals. In study M068-95 at 100mg/kg/day, significantly lower thyroid weights were observed in female animals. A 2.5-cm mass was observed in the spleen of one male animal, but was considered unrelated to drug treatment. Plasma drug concentrations were sampled 3 hours post-dosing, once during week 4 and once during week 12/13 for each of the 3 studies, but the lack of adequate toxicokinetic data with respect to AUC and Cmax, impede exposure assessments.

Chronic repeat-dose toxicity data to support the eflornithine component is reported from 52 week dog (Report 560-033) and rat (Report 560-032) studies, in which eflornithine was administered orally to rats

at doses of 0, 400, 800 and 1600 mg/kg/day and orally to dogs at doses of 50, 100 and 200 mg/kg/day. These study reports include statements indicating that the studies were conducted in compliance with the FDA, GLP Regulation of 1979 and as modified by the final rule effective October 5, 1987. Therefore, while these studies are not considered compliant with current OECD GLP standards, they may be considered of an acceptable standard. In rats, cumulative body weight gain in the 1600 mg/kg/day group was 26.4% lower than control for males and 23.0% lower for females, this was associated with decreased food consumption. Rats receiving 800 or 1600 mg/kg/day exhibited dermatological reactions, including alopecia, dermatitis (scabs on head and lips) with dose-dependent increasing incidence over time (females more affected than males). Trace to mild liver necrosis in male rats, and trace to mild inflammation in the glandular stomach (primarily in males) was also reported. A no observed effect level (NOEL) for rats identified in this study was 400 mg/kg/day. However, no toxicokinetic data are included and therefore exposure at this dose level is unknown.

In dogs, dose-dependent findings including alopecia, dermatitis around the eyes, ears, and neck, and ocular discharge with mild to moderate thickening of the conjunctiva that were observed in all of the treated dosage levels throughout the study. In addition, diarrhoea and soft stool were seen more often in the treated than in the control dogs throughout the study. The sponsor considers the observed toxicities in dogs were related to pharmacological activity of eflornithine and not serious, and suggests a safety factor of 2.2 to a marketed dose of 750 mg (assuming a 60kg human), but a NOEL was not defined for this study and no toxicokinetic data are available.

No toxicokinetics are available from these chronic repeat-dose toxicity studies and the relevance of the findings from these studies to clinical safety is difficult to interpret. The applicant has provided supportive supplementary data on the pharmacokinetics of eflornithine in various species that indicate relevant exposures were likely achieved in these non-clinical species, although the safety margins cannot be calculated. Considering the totality of the available clinical and non-clinical data and in the interests of 3Rs, additional non-clinical chronic toxicity data will not be considered necessary.

Sulindac studies:

The repeat-dose toxicity information provided for sulindac is referenced entirely from the sulindac FDA Summary Basis of Approval, a publicly available assessment report. No repeat-dose toxicity data has been provided. As outlined in the Notice to applicant Volume 2A, "*It must be stressed that assessment reports such as the EPAR for EU marketing authorisations or similar summary reports from competent authorities inside and outside the EU which are made publicly available by competent authorities for reasons of transparency cannot be considered to meet the requirements of Annex I of Directive 2001/83/EC*." Therefore, the available non-clinical information is not considered sufficient to support an appropriate non-clinical safety assessment of sulindac for chronic use in Flynpovi. However, the adverse event profile of NSAIDs, including Cox-2 inhibitors, is known. The target organs are kidney (degenerative nephropathy, papillary necrosis), liver (fibrosis, inflammatory periportal cell infiltration, bile duct proliferation, small focal necrosis), stomach and intestine (ulceration, erosion), haematologic tissue. Gastrointestinal adverse events, including serious events of PUB (perforation, ulcer, bleeding) are one main reason for discontinuation of treatment with NSAIDs. Other events such as hypersensitivity or skin reactions, cardio-renal effects and hepatotoxicity are class effects. Therefore, this deficiency in the non-clinical dossier for sulindac could be acceptable on the basis of the extensive clinical experience with sulindac, provided that re-assurance on the long term safety of Flynpovi is provided.

Combination of eflornithine and sulindac:

No repeated dose toxicity studies are performed with the combination eflornithine and sulindac. ICH M3(R2) indicates for two late stage products for which there are no causes for significant toxicological concern based on the available data, but there is no adequate clinical experience with the co-administration of both components together, non-clinical combination studies are recommended

before marketing. Both eflornithine alone and sulindac alone had toxic effects on stomach and intestine, liver and haematologic tissue, but it is unknown whether the combination has additive effects on these or other toxicities. Furthermore, as outlined in ICH S3A, systemic exposure in toxicity studies should be estimated in an appropriate number of animals and dose groups to provide a basis for risk assessment. For eflornithine, repeat-dose toxicity studies are reported in mice, rats, dogs and monkeys but plasma eflornithine concentrations at very limited timepoints are the only toxicokinetic data presented, AUC and Cmax, are not reported for any study. Also, no sulindac toxicokinetics are reported and no combination data are available. In the absence of toxicokinetic data to support risk assessment based on the repeat-dose studies/ information provided for eflornithine and sulindac, the relevance of the findings from these studies to clinical safety is difficult to interpret. A non-clinical combination toxicology study will not be requested at this stage in development, as clinical data on the combination is available.

## *Genotoxicity*

Eflornithine:

No genotoxicity studies for eflornithine were conducted by the applicant. However 3 study reports and 2 articles from the scientific literature were submitted in support of this application.

**Table 1: Summary of genotoxicity studies submitted**

| Study Type | Species/Cell System | Doses | Result | Reference or Study No. |
|---|---|---|---|---|
| Bacterial reverse mutation assay | *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 | 0.030–5.0 mg/plate | Treatment with eflornithine is not mutagenic | v-83-01 |
| Chromosomal Analyses | BHK and Vero cells | 1.0–2.5 mM for 7 and 12 days | Eflornithine treated cell lines did not show significantly greater number of chromosome aberrations than the control treated cell lines. | Pohjanpelto et al, 1988 |
| Micronucleus Assay (in vivo) | Bone marrow cells from Chinese hamsters | 30–40 mg/kg/day for 21 days | No increase in the frequency of chromosomal abnormalities or decreased frequency of mitosis was observed in bone marrow cells from hamsters with eflornithine treatment | Pohjanpelto et al, 1988 |
| Point mutation test | *Schizosaccharomyces pombe* | 250 to 2000 mg/mL | No increase in mutant frequency was observed at any concentration of eflornithine, either with or without metabolic activation | Study v-82-06 |
| DNA repair test | *Saccharomyces cerevisiae* | 250 to 2000 mg/mL | No increase in convertant frequency was observed at any concentration of eflornithine, either with or without metabolic activation | Study v-82-07 |

Abbreviations: po = oral (per os)

Eflornithine was negative for mutagenicity in an Ames test (study v-83-01) with and without metabolic activation (aroclor-induced rat liver S9). Similarly, no mutagenic activity is reported in a point mutation *test in vitro* in the yeast *Schizosaccharomyces pombe*, either with or without metabolic activation, at concentrations up to 2 mg/ml (study v-82-06). Furthermore, supportive information from the SmPC of Vaniqa (eflornithine: standard genotoxicity test battery *in vitro* and *in vivo*) specifies that eflornithine has no genotoxic potential. Moreover, eflornithine caused severe chromosome aberrations in mammalian cells *in vitro*, under the condition of extensive polyamine depletion. The applicant submitted 2 negative Ames tests (v-83-01), but these were non-GLP compliant. These data are supported by negative findings in mutagenicity tests conducted in yeast (v-82-07 and v-82-06), also non-GLP compliant.

Sulindac:

The applicant has not conducted any genotoxicity studies and no study reports were submitted to support the genotoxicity assessment for sulindac. The applicant only provided supportive information from the Sulindac ex-US product monograph (TEVA, 2011), the Sulindac Product Insert (Actavis May 2016), and a single bibliographic reference describing a protective effect of sulindac sulfide against radiation induced genotoxicity and DNA damage in human blood samples obtained from healthy volunteers at doses ranging from 10-250 µM (Torabizadeh et al. 2019). The applicant proposed to provide the required complete battery of genotoxicity tests for sulindac post-authorisation, but this is

not considered acceptable as the genotoxicity assay is required to inform the safety assessment of the sulindac component of Flynpovi.

Combination of eflornithine and sulindac:

The absence of combination genotoxicity studies could be acceptable provided the genotoxicity of the mono-components is adequately addressed.

## *Carcinogenicity*

Eflornithine:

In mice, results from a 2-year carcinogenicity study with eflornithine administered in the diet at 100, 300, and 1000 mg/kg, demonstrated no treatment-related neoplastic or non-neoplastic histopathologic lesions and no indication of carcinogenic effects in any organ in male and female mice following eflornithine treatment.

In the rat study, an increased incidence in mononuclear cell leukaemia in males and females treated with eflornithine is reported, relative to the incidence in the vehicle control group. The applicant does not consider it likely that this is treatment-related on the basis that the incidence was reportedly within or only slightly greater than the historical control incidence of this lesion in Fisher-344 rats, that historical data for this lesion demonstrated wide variability and considering there was no clear dose response pattern in eflornithine-treated rats.

An increased incidence of pancreatic islet cell adenoma and oral mucosal squamous cell carcinoma are also reported in the eflornithine–treated rats, which the applicant considered could be related to eflornithine treatment. The possibility of carcinogenic risk with eflornithine cannot be excluded on the basis of the data presented. Therefore, the findings of possible treatment-related increased incidence of pancreatic islet cell adenoma and oral mucosal squamous cell carcinoma in rats were included in section 5.3 of the SmPC.

The toxicokinetic data from the two eflornithine carcinogenicity studies are limited to mean plasma eflornithine concentrations at only 3 and 4 timepoints in the mouse and rat study respectively, across the 104-week administration periods. The choice of timepoint has not been justified and there is only one common collection timepoint (18 months) used in both studies. AUC and Cmax, are not reported for either study therefore limiting exposure assessments and interspecies comparisons. The plasma drug concentration reported in mice after 18 months of eflornithine administration at 1000 mg/kg/day is 59.4 µg/ml and 33.23 µg/ml for males and females respectively. The plasma drug concentration reported in rats after 18 months of eflornithine administration at 600 mg/kg/day is 1192 µg/ml and 1492 µg/ml for males and females respectively. However, it is unclear that these plasma drug concentrations reported in mice and rats after 18 months of eflornithine administration represent a Cmax and therefore it is difficult to compare exposures.

Sulindac:

Supportive information has been provided by the applicant regarding the carcinogenicity assessment of Sulindac, referenced from the Sulindac ex-US monograph (TEVA, 2011), the Summary basis of Approval (SBA) for Clinoril (FDA, 1978) and the Sulindac Package Insert (Actavis May 2016). The available information relates to an 81-week study in mice administered 0, 5, 10, 20 mg/kg/day sulindac and a 104-week study in rats administered 0, 5, 10, 20 mg/kg/day sulindac, submitted to the FDA in 1977. These studies pre-date the FDA GLP Regulation of 1979. The quality of these data cannot be assessed as the study reports are not available and there is no information regarding exposures achieved for either study. However, there are some details included in the SBA worth noting, including a significantly higher

incidence of myeloid hyperplasia in the spleen, bone marrow and lymph nodes of mice treated with the high dose of 20 mg/kg/day sulindac for 81-weeks. The sponsor reportedly submitted additional slides from this dose group and control animals in response to a query raised by the FDA on these data and reported that there was no evidence of transformation of neoplasia from hyperplasia in these mice (Clinoril SBA 1978). Of particular interest, a low incidence of metastatic leukaemia in the kidney, spleen, lymph node and/or bone marrow was reported in the 105-week carcinogenicity study in rats at 20 mg/kg/day (4%) which was not significantly higher than control groups (2%). An insufficient number of rats in the mid and low dose group were reportedly examined microscopically, but an incidence of 5% for the 10 mg/kg group and 2% for the 5 mg/kg group is estimated. The FDA concludes that although they accepted the sponsor's conclusion that the incidence of leukaemia was a chance occurrence, they also remarked that in the range of incidence rats observed (2-5%), doubling the incidence rate produces differences in rates that are small, thus yielding low power, indicating that the sample size is insufficient to detect a significant difference of 3%.

The applicant has also provided one literature reference, describing a large retrospective screening study for possible carcinogenic effects associated with commonly used prescription drugs, not previously screened for carcinogenic effects (Friedman et al. 2009). The study identified 112,292 patients in the Kaiser Permanente Medical Care Program that received sulindac for a median treatment duration of 6 months. The authors conclude that there was likely biological connection between sulindac treatment and gallbladder cancer (n=9, RR [95% CI] =2.88 [1.34-6.19]) and leukaemia (n=5, RR [95% CI] =5.78 [1.88-17.78]). The authors consider this a likely biological connection due to the excretion of sulindac in bile, the presence of sulindac metabolites in gallstones and the association between gallstones and a predisposition to gallbladder cancer. The authors suggest that further research is needed to address whether sulindac increases the risk of gallstones, whether the presence of sulindac metabolites in gallstones increases their carcinogenicity, or whether sulindac in bile increases risk of both stones and cancer without stones as a necessary intermediate step to cancer. Furthermore, of the five cases of Other Leukaemia reported, the specific diagnoses in the Cancer Registry were: three "Leukaemia, not otherwise specified", one "Acute Leukaemia, not otherwise specified" and one "Aggressive NK- (natural killer) cell leukaemia". The authors indicate that there have been a few case reports of adverse effects on the bone marrow attributed to sulindac, for which they provide references. These included aplastic anaemia, erythroblastopenia, and progression of leukopenia to aplastic anaemia and acute myeloid leukaemia. The authors acknowledge that the relevance of these findings to their observation is unknown, but they suggest that it may add to the desirability of further studies of sulindac and cancer risk.

Based on the presented data, including the metastatic leukaemia finding in rat and the clinical data from Friedman et al. (2009) indicating an association with leukaemia and gall bladder cancer, the submitted information were not considered sufficient to rule out a potential signal of concern for chronic use of sulindac and a thorough weight of evidence assessment of the potential carcinogenicity of sulindac was requested during the evaluation. During the procedure, the applicant highlighted that the risk of developing leukaemia and gallbladder cancers identified in the Friedman study is low (0.008%, from >112,000 patients) and that in 2020 the global incidence of gallbladder cancer was 0.0149% (115,494/7.8 billion) and leukaemia was 0.0608% (474,519/7.8 billion), both of which are higher than what was observed by Friedman et al. The applicant also highlighted that the Friedman article did not include or discuss if these patients had other pre-existing or concurrent conditions that would predispose them to cancer.

Combination of eflornithine and sulindac:

In accordance with ICH M3, combination carcinogenicity studies generally are not recommended to support marketing if the individual agents have been tested according to current standards. The sponsor received Scientific advice (EMA/CHMP/SAWP/301490/2015) from CHMP in May 2015 regarding the adequacy of a historical review of carcinogenicity studies of eflornithine and sulindac as single agents, to

address the carcinogenicity assessment for the fixed dose combination product. The CHMP advised that additional carcinogenicity studies would not be required provided the applicant could provide study reports or publicly available literature to support the carcinogenicity assessment of the individual agents, reference to publicly available assessment reports would not be sufficient. It was noted that for sulindac it was not entirely clear from the provided dossier what carcinogenicity studies, if any, are available in the public domain.

## *Reproduction Toxicity*

Eflornithine: Data from the literature indicate that eflornithine (200 mg/kg) did not affect implantation in pregnant hamsters administered 200 mg/day during pre-implantation (day 1-3), while administration for 5 days post-implantation (days 4-8) resulted in 100% pregnancy termination (Galliani et al., 1983). Similarly, eflornithine (200 mg/kg bid) administered to rats on day 4-7 of pregnancy inhibited embryogenesis and no pups were delivered, but administration on days 1-3 of pregnancy had no effect (Reddy and Rukmini, 1981).

The applicant has provided study reports to support an assessment of embryo-foetal development in rats and rabbits, including dose-range finding (studies 207 and 209) and pivotal studies (studies 210 and 211), with eflornithine administered from implantation to closure of the hard palate in both species. These pivotal studies include statements indicating GLP-compliance and are considered acceptable. In rats, maternal toxicity was reported at doses ≥ 800 mg/kg/day and developmental toxicity at doses ≥ 200 mg/kg/day, with significantly decreased foetal weights and increased incidence of litters with skeletal variations of 14th rudimentary rib, 14th full rib, and/or 27th pre-sacral vertebrae. A NOEL for maternal toxicity of 200 mg/kg/day and a foetal toxicity NOEL of 80 mg/kg/day is reported in rats. In rabbits, developmental toxicity in the absence of maternal toxicity was reported at 135 mg/kg/day, with slightly increased early resorptions, decreased implantation sites, decreased viable foetuses, and reduced foetal weights. There were no external, visceral, or skeletal anomalies at any dose level. A NOEL for maternal toxicity of 135 mg/kg/day and a foetal/developmental NOEL of 45 mg/kg/day is reported data are reflected in section 5.3 of the SmPC.

The applicant has also provided a study report for a PPND study, which includes a GLP compliance statement, dated 1986 (study T-86-20), this is not considered indicative of compliance with current OECD GLP standards. Eflornithine was administered orally (in drinking water) to rats from GD 15 to postnatal (PN) day 21 at concentrations of 0.1, 0.3 or 1% eflornithine (equivalent to doses of 167, 480 and 1329 mg/kg/day). Maternal toxicity (reduced maternal weight gain and reduced food consumption) was reported at ≥ 480 mg/kg/day, but no adverse effects on maternal reproductive parameters were noted. Foetotoxicity was also reported at ≥ 480 mg/kg/day, with significantly reduced pup weight during nursing, which continued throughout the growth period after weaning in female pups but lasted only 5 weeks in high dose males. No significant effects on behaviour, development, or reproductive function of the F1 offspring was reported, with the exception of a reduced fertility index in the high dose group (76.5% vs 89.5%) which the authors considered of questionable biological significance.

Sulindac:

Minimal information has been provided by the applicant regarding the reproductive and developmental toxicity assessment of sulindac. This information consists of 2 paragraphs of text copied from the Sulindac ex-US product monograph (TEVA 2011), together with reference to the FDA-approved product labelling for Clinoril (sulindac) tablets (Merck, 2010) and one literature reference (Hucker et al. 1973).

Information from the TEVA 2011 product monograph indicates foetotoxicity on PND 1 in rats at clinically relevant dose levels (1.3 and 2.6 times the maximum recommended daily dose in humans), but no exposure information is available. Prolonged gestation was also noted in rats and an association between

NSAIDS and increased incidence of dystocia and delayed parturition in pregnant animals is also mentioned. Inconsistent findings of visceral and skeletal malformations observed in rabbits are also reported, although no further study details are available to interrogate these findings and this information is considered supportive in the absence of the underlying study reports.

The applicant references a recommendation against use in pregnancy (particularly late pregnancy) from the FDA-approved product labelling for Clinoril (Merck 2010), due to the risk of premature closure of the ductus arteriosis. The applicant also reports no effect on reproductive performance in either male or female rats at a dose level up to 40 mg/kg/day, referenced from the Clinoril product label (Merck, 2010). Finally, a single literature reference has been provided, indicating that sulindac crosses the placental barrier in the rat to a minimal degree and was excreted to a minor extent in rat milk (Hucker et al. 1973).

Section 4.3 of the proposed SmPC for Flynpovi includes a contraindication in pregnancy with appropriate referencing to section 4.6, which is considered acceptable. Furthermore, section 4.6 of the proposed Flynpovi SmPC indicates that use of NSAIDs, including sulindac, during the third trimester of pregnancy increases the risk of premature closure of the foetal ductus arteriosus. This is also acceptable on the basis of the known risk associated with NSAID use in late pregnancy.

Section 4.6 of the proposed SmPC also indicates that the use of sulindac may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Flynpovi should be considered. This is acceptable on the basis of the known transient risk to female fertility associated with NSAID use.

Regarding breastfeeding, section 4.6 of the proposed SmPC indicates that it is not known whether Flynpovi is excreted in human milk. However, sulindac is secreted in the milk of lactating rats. Because of the potential for serious adverse reactions in nursing infants from Flynpovi, a decision should be made whether to discontinue breast-feeding or to discontinue/abstain from the Flynpovi therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. This is acceptable on the basis of the literature refererence (Hucker et al, 1973) which examines the disposition and metabolic fate of sulindac in rats, dog and rhesus monkey and man. This article indicates that 2 and 4 hours following an oral dose of 10 mg/kg of 14C-sulindac, rat milk contained 3.8 ug/ml and 5.4 ug/ml equivalents respectively, compared to 33.8 ug and 29.7 ug in plasma respectively, suggesting rat milk contained approximately 10 to 20% of plasma levels of sulindac.

In summary, the data provided by the applicant to assess the reproductive and developmental toxicity of sulindac consists only of supportive information from the TEVA 2011 product monograph, the FDA-approved labelling for Clinoril (sulindac) tablets and a single literature reference from 1973. However, section 4.3 of the SmPC for Flynpovi includes a contraindication in pregnancy and section 4.6 includes a warning for women of child bearing potential (WOCBP) to use contraception during and for up to 2 weeks after treatment with Flynpovi. In addition, there is a relevant class effect regarding risks associated with the use NSAIDs in pregnancy, and wording related to the risks associated with NSAID use in the third trimester of pregnancy is included in section 4.6 of the SmPC. Therefore, the lack of suitable reproductive and developmental toxicity data to support an appropriate safety assessment for Flynpovi will not be further pursued in the interests of 3Rs principles, as further studies are considered unlikely to affect the understanding of the risk associated with the use of this product and unlikely to significantly affect the labelling.

Combination of Eflornithine and Sulindac:

No combination reproductive and developmental toxicology data have been provided, which may be acceptable where the reproductive and developmental toxicity profiles of the single compounds are sufficiently characterised.

### *Other toxicity studies*

The applicant has included data from the literature regarding eflornithine-induced hearing loss. It is reported that eflornithine produced hearing loss in adult guinea pigs treated for 12 week with 1% eflornithine (an approximate dose of 1600 mg/kg/day), or for 8 weeks with 1.3% eflornithine in drinking water, and the magnitude of the loss increased during the treatment period. The association with eflornithine use and hearing impairment is incorporated into the proposed label, as are precautions for the use of eflornithine.

## 2.3.5. Ecotoxicity/environmental risk assessment

No new studies on the combination have been performed. LogKow values obtained from publicly sourced literature have been submitted.

The applicant has applied a revised Fpen (0.2 in 10000) in the PEC calculation using disease prevalence data submitted and accepted in the orphan drug designation. This is considered acceptable and in line with the answer to question 4 of the ERA Q and A document. The calculated PEC values utilising this modified Fpen are below the action limit and therefore no phase II assessment is required.

**Table 2**: **Summary of main study results**

| **Substance (INN/Invented Name): Sulindac** | | | |
|---|---|---|---|
| **CAS-number (if available): 38194-50-2** | | | |
| ***PBT screening*** | | Result | **Conclusion** |
| *Bioaccumulation potential*- log $K_{ow}$ | shake-flask method | -0.6 @ pH 7.4 | Potential PBT (N) Applicant has committed to supply appropriate data post-marketing |
| ***PBT-assessment*** | | | |
| **PBT-statement :** | The compound is considered as PBT (additional data requested) | | |
| ***Phase I*** | | | |
| ***Calculation*** | **Value** | **Unit** | **Conclusion** |
| PEC $_{surfacewater}$ , default or refined (e.g. prevalence, literature) | 0.0015 | µg/L | > 0.01 threshold (Y/N) |
| Other concerns (e.g. chemical class) | | | (N) |

| **Substance (INN/Invented Name): Eflornithine** | | | |
|---|---|---|---|
| **CAS-number (if available): 70052-12-9** | | | |
| ***PBT screening*** | | Result | **Conclusion** |
| *Bioaccumulation potential*- log $K_{ow}$ | Shake-flask method | -2.1 | Potential PBT (N) Applicant has committed to supply appropriate data post-marketing |
| ***PBT-assessment*** | | | |
| **PBT-statement :** | The compound is considered as PBT (additional data requested) | | |
| ***Phase I*** | | | |
| ***Calculation*** | **Value** | **Unit** | **Conclusion** |
| PEC $_{surfacewater}$ , default or refined (e.g. prevalence, literature) | 0.0074 | µg/L | > 0.01 threshold (Y/N) |
| Other concerns (e.g. chemical class) | | | (N) |

## 2.3.6. Discussion on non-clinical aspects

*Pharmacodynamics*

No new primary pharmacodynamics studies have been submitted with the current application with the applicant instead relying on data from the publicly available literature. One study submitted using a mouse model heterozygous for the APC gene reports that sulindac administration is associated with an increase in tumour burden in the colon of these animals. Submission of data from other animal models of colon carcinogenesis suggest this may be a model specific effect and this finding is not considered of clinical relevance. Only a single in-vivo study examining the effect of co-administration of eflornithine and sulindac in the $Apc^{Min/+}$ mouse model has been submitted and no difference in terms of efficacy at reducing tumour burden between the combination and mono-component groups were observed. Of note, in this study, sulindac alone (167 ppm in diet) produced the numerically greatest reduction in tumour number/animal, but was also associated with the highest total polyamine levels. No correlation between small intestine total polyamine levels and tumour or high grade adenoma incidence were evident, but it should be noted that polyamine levels in this study were highly variable. These data do not support the proposed mechanism of action, nor are they considered to support a synergistic effect on total tumour burden in this model. Therefore, no non-clinical data have been submitted demonstrating the additive effect of the proposed FDC over the mono-components. The efficacy and benefit risk of the proposed FDC will be based exclusively on the available clinical data.

Given the reported Cmax for sulindac at 750 mg is 40 µM, the CHMP concluded that this does not indicate a significant cause for concern with regard to QT prolongation. The submitted assessment of safety pharmacology is not considered sufficient in line with the requirements set out in ICH 7A or B.

*Pharmacokinetics*

No dedicated *in vivo* non-clinical PK studies have been submitted by the applicant. Older toxicology studies conducted with eflornithine have been submitted with this application. These predate current guidance but do not contain adequate information on the validation of the methods used for the analysis of eflornithine concentrations in PK samples taken to confirm adequate systemic exposure. Only a single sampling time point was used in these studies which means that PK parameters like AUC, t1/2, Cmax and Tmax cannot be derived. This makes direct comparison to clinical exposures problematic. The applicant has conducted a number of dedicated in-vitro studies to assess the potential for eflornithine DDI at CYP450 and UGT enzymes and relevant human transporters which do not suggest a cause for concern.

Sulindac is not a substrate for P-glycoprotein, and the cytochrome P-450 isoforms 3A4, 2C9, 2D6, 2C19, and 3A4. It is a known inhibitor for cytochrome P-450 1A1 and 1A2, MRP-2, MRP-4, OAT-1 and OAT-3 (http://www.drugbank.ca/drugs/DB00605) (El-Shiekh 2007; Khamdang et al. 2002; Rius et al. 2003). Additionally, Lee et al., recently characterised the inhibition of multiple transport proteins by sulindac and its metabolites in rat and human hepatocytes. Results demonstrated inhibition of NTCP, OATP, BSEP, and BCRP by sulindac, sulindac sulphide, and sulindac sulfone (Lee, Paine, and Brouwer 2010).

*Toxicology*

In support of this MAA, the applicant relies on non-clinical toxicology data for the mono-components eflornithine and sulindac. The submitted non-clinical data is not considered sufficient to support an adequate non-clinical safety assessment of Flynpovi and the deficiencies in the non-clinical genotoxicity assessments for the mono-components are considered of major importance.

In general, the applicant has provided a circular argument for the omission of the combination toxicology study, and the deficiencies in the submitted data on the mono-components. The applicant argues that data on the individual active substances are not required to support an Article 10(b) application for a fixed dose combination product. This may be acceptable where combination data are sufficient, but the

applicant has not provided any non-clinical data on the combination. The applicant justifies the absence of non-clinical combination data on the basis of well-established use of the mono-components. However, the applicant's position that the mono-components have well-established medicinal use is not agreed. As outlined in the Notice to Applicant Volume 2A Chapter 1, "*Well-established use refers to the use for a specific therapeutic use. If well-known substances are used for entirely new therapeutic indications and it is not possible to solely refer to a well-established use, then additional data on the new therapeutic indication together with appropriate pre-clinical and human safety and/or efficacy data should be provided*." In the absence of sufficient well-documented clinical experience to establish all aspects of clinical efficacy and safety with the combination, non-clinical studies are required. The applicant has not provided adequate non-clinical data on the individual active substances to support an appropriate non-clinical assessment, or to justify the absence of non-clinical combination data and the well-established use status of the mono-components is not agreed. Therefore, in the absence of non-clinical combination toxicology data, deficiencies in the mono-component data must be adequately addressed.

For eflornithine, the applicant did not submit any toxicokinetic data for studies 560-032 and 560-033 and a discussion regarding exposure margins from these chronic repeat-dose toxicity data with eflornithine to the intended clinical use of Flynpovi was requested. The applicant could not provide the requested toxicokinetic data for the chronic repeat dose toxicity studies conducted with eflornithine in rats and dogs. Instead, the applicant has provided supportive supplementary data on the pharmacokinetics of eflornithine in various non-clinical species following single administration of eflornithine. The applicant argues that there is no accumulation of eflornithine over time and linearity of exposure. The provided supportive data indicate relevant exposures were likely achieved in these non-clinical species, although the safety margins presented are not accepted. Considering the totality of the available clinical and non-clinical data and in the interest of 3Rs, additional non-clinical chronic toxicity data are not requested.

The applicant has also not submitted sufficient data to conclude that eflornithine is not genotoxic *in vivo* at relevant exposures for FAP patients administered Flynpovi. As outlined in ICH S2 (R1), an *in vivo* test for genotoxicity, generally a test for chromosomal damage using rodent haematopoietic cells, either for micronuclei or for chromosomal aberrations in metaphase cells would be required.

The applicant reported equivocal findings from the non-conventional studies of clastogenicity but considers that eflornithine causes severe chromosomal damage only where severe polyamine depletion occurs and does not anticipate this to be an issue at plasma concentrations associated with Flynpovi administration where the polyamine pathway is functional. The applicant provides the Vaniqa product label as supportive information that eflornithine is not genotoxic but has not adequately addressed the question regarding the exposure achieved in the dermal micronucleus assay conducted with eflornithine. The applicant has not submitted sufficient data to conclude that eflornithine is not genotoxic *in vivo* at relevant exposures for FAP patients administered Flynpovi, the applicant proposed to submit an *in vivo* test for genotoxicity of eflornithine as a post-authorisation commitment and prior to placing on the market, but post-authorisation submission of required genotoxicity data is not considered acceptable as the outcome of this genotoxicity study is required to inform the non-clinical safety assessment of Fflynpovi, the non-clinical dossier cannot be considered complete in the absence of these data.

For sulindac, a complete battery of genotoxicity tests is required in accordance with ICH S2B. The applicant did not provide the required data but proposed to conduct these studies post-authorisation prior to the placing on the market. This proposal is not acceptable as the outcome of these genotoxicity studies are required to inform the non-clinical safety assessment of Flynpovi. The absence of adequate genotoxicity data to support Flynpovi precludes an approval.

An increased incidence in mononuclear cell leukaemia in males and females rats treated with eflornithine vs control was reported. Given that the incidence was reportedly within or only slightly greater than the

historical control incidence of this lesion in Fisher-344 rats, that historical data for this lesion demonstrated wide variability and considering there was no clear dose response pattern in eflornithine-treated rats, it is agreed that this finding is likely not treatment related. Based on the totality of the data presented regarding the carcinogenicity assessment for sulindac, including the metastatic leukaemia finding in rat and the clinical data from Friedman et al. (2009) indicating an association between sulindac use and leukaemia and gall bladder cancer, the submitted information are not considered sufficient to rule out a potential signal of concern for chronic use of sulindac. A weight of evidence assessment to address the carcinogenicity of sulindac following chronic use was requested during the evaluation. During the procedure, the applicant highlighted that the risk of developing leukaemia and gallbladder cancers identified in the Friedman study is low (0.008%, from >112,000 patients) and that in 2020 the global incidence of gallbladder cancer was 0.0149% (115,494/7.8 billion) and leukaemia was 0.0608% (474,519/7.8 billion), both of which are higher than what was observed by Friedman et al. The applicant also highlighted that the Friedman article did not include or discuss if these patients had other pre-existing or concurrent conditions that would predispose them to cancer. Based on the totality of the data presented, considering the extent of clinical experience with sulindac, the lack of long-term clinical safety data with chronic use of sulindac and in the absence of adequate genotoxicity data, the current non-clinical data are considered insufficient with respect to carcinogenicity but further carcinogenicity studies will not be requested. The applicant was asked to amend section 5.3 of the SmPC to reflect this, the applicant did not implement the requested change and this point therefore remains unresolved.

*Environmental risk assessment*

PEC surfacewater value for both actives is below the action limit of 0.01 µg/L. Data submitted suggest is not a PBT substance as log Kow does not exceed 4.5. The environmental risk assessment provided with this application is considered incomplete by the CHMP as the submitted LogKow values for both monocomponents are not derived from appropriately conducted OECD compliant studies in line with the requirements set out in the EMAs 'Guideline on the Environmental Risk Assessment of Medicinal Products of Human Use' (EMEA/CHMP/SWP/4447/00 corr 2)..

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of Sulindac and eflornithine to the environment.

### 2.3.7. Conclusion on the non-clinical aspects

The non-clinical dossier is incomplete, which precludes a recommendation for marketing authorisation. The applicant has not submitted sufficient non-clinical data to support an adequate non-clinical genotoxicity assessment for Flynpovi. The applicant was asked to amend section 5.3 of the SmPC to reflect that non-clinical data are considered insufficient with respect to carcinogenicity assessment for sulindac, the applicant did not agree to implement the requested change to the product information and this issue therefore remains outstanding.

## *2.4. Clinical aspects*

### 2.4.1. Introduction

### *GCP*

The applicant has provided a statement to the effect that clinical trials conducted outside the Community

were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

| Type of Study | Study Identifier | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s) and Dose | Number of Subjects | Population | Duration of Treatment |
|---|---|---|---|---|---|---|---|---|
| **Efficacy and Safety Studies** | | | | | | | | |
| Efficacy/ Safety, PK sub-study | CPP-FAP-310 | 5.3.5.1 | Determine whether the combination of oral eflornithine + sulindac is superior to either eflornithine or sulindac single-agent treatment in delaying the time from the date of randomization to the date of the first occurrence of any FAP-related event | Phase 3, double-blind, randomized | • Eflornithine + sulindac single agent tablets (250 mg /150 mg, oral tablets), 750 mg/150 mg daily dose (n=56)<br>• Placebo + sulindac single agent tablets (150 mg, oral tablets), 150 mg daily dose (n=58)<br>• Eflornithine + placebo single agent tablets (250 mg oral tablets), 750 mg daily dose (n=57) | 171 | FAP patients | Up to 48 months |
| | CPP-FAP-310 Sub-study | 5.3.5.1 | Determine the pharmacokinetic profile of eflornithine, sulindac, or eflornithine + sulindac in FAP patients from 0 to 8 hours after administration | Phase 3, double-blind, randomized | • Eflornithine + sulindac single agent tablets (250 mg /150 mg, oral tablets), 750 mg/150 mg daily dose (n=50) | 155 | FAP patients | Single dose at the 3-month clinical visit |

| Type of Study | Study Identifier | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s) and Dose | Number of Subjects | Population | Duration of Treatment |
|---|---|---|---|---|---|---|---|---|
| | | | | | • Placebo + sulindac single agent tablets (150 mg, oral tablets), 150 mg daily dose (n=51)<br>• Eflornithine + placebo single agent tablets (250 mg oral tablets), 750 mg daily dose (n=54) | | | |
| Efficacy/ Safety | Pharmaco-prevention of Sporadic Colorectal Adenomas | 5.3.5.1 | • Determine whether the combination of oral eflornithine (500 mg or 0.2 g/m$^2$) plus sulindac (150 mg) reduces the occurrence of metachronous colorectal neoplasia (incidence of colorectal adenomas, cancer) detected by standard colonoscopy | Double-blind, randomized, placebo-controlled | • Oral eflornithine + sulindac (500 mg tablet or 0.2 g/m$^2$ solution +150 mg), n=191<br>• Placebo, n=184 | 375 | Individuals at increased risk of colorectal carcinoma and adenomatous polyps in the colon | 36 months |
| | CAT-001, updated analysis report of the Pharmaco-prevention of Sporadic Colorectal Adenomas study | 5.3.5.1 | • Determine whether the combination of oral eflornithine (500 mg or 0.2 g/m$^2$) plus sulindac (150 mg) reduces the occurrence of metachronous colorectal neoplasia (incidence of colorectal adenomas, cancer) detected by standard colonoscopy<br>• Updated efficacy analysis of the ITT population<br>• Addresses missing data from original study analysis<br>• Assesses Type I error not adjusted for interim analysis<br>• Recoding of safety data to MedDRA 15.1 | Double-blind, randomized, placebo-controlled | • Oral eflornithine + sulindac (500 mg tablet or 0.2 g/m$^2$ solution +150 mg), n=191<br>• Placebo, n=184 | 375 | Individuals at increased risk of colorectal carcinoma and adenomatous polyps in the colon | 36 months |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Pharmacokinetics and Bioequivalence Studies** | | | | | | | |
| PK – renal impairment | ELA-P4-466 | 5.3.3.3 | To evaluate the PK profile of eflornithine following a single oral 750 mg dose in subjects with normal and impaired renal function | Open-label, non-randomized parallel-group, adaptive, single dose | Eflornithine (250 mg film-coated tablets), single 750 mg dose | 32 | Healthy subjects, subjects with mild, moderate, or severely impaired renal function (n=8 per group) | Single dose |
| PK - pilot BE | CPP-P9-658 | 5.3.1.2 | To compare the PK parameters of eflornithine, sulindac, sulindac sulfide, and sulindac sulfone in plasma following oral administration of a co-formulated tablet or single agent tablets | Single dose, randomized, open-label, four-period, four-sequence, crossover | • Eflornithine /Sulindac fixed-dose combination (375 mg /sulindac 75 mg, oral tablet, ES-FDC), single 750 mg/150 mg dose<br>• Eflornithine (250 mg, oral tablet), single 750 mg dose<br>• Sulindac (150 mg, oral tablet), single 150 mg dose | 12 | Healthy subjects | Single dose, each followed by 7-day washout between periods |
| | | | | | • Eflornithine + Sulindac single agent tablets (250 mg / 150 mg, oral tablets, respectively), single 750 mg/150 mg dose | | | |
| PK – BE/FE | CPP-P6-366 | 5.3.1.2 | To compare the PK parameters and comparative bioavailability and food effect of eflornithine, sulindac, sulindac sulfide, and sulindac sulfone in plasma following oral administration of a co-formulated tablet under fed and fasting conditions | Single dose, randomized, four-period, four-sequence, crossover | • Eflornithine/ Sulindac fixed-dose combination (375 mg /sulindac 75 mg, oral tablet, ES-FDC), single 750 mg/150 mg dose, fed conditions<br>• Eflornithine/ Sulindac fixed-dose combination (375 mg /sulindac 75 mg, oral tablet, ES-FDC), single 750 mg/150 mg dose, fasted conditions | 92 | Healthy subjects | Single dose, each followed by 7-day washout between periods |

## 2.4.2. Pharmacokinetics

The current application is for a co-formulated eflornithine/sulindac fixed dose combination (FDC) tablet which is indicated as an adjunct to standard of care for treatment of adult patients with Familial Adenomatous Polyposis (FAP). The proposed daily dose is 750 mg eflornithine and 150 mg sulindac (2 tablets taken once daily with food).

Four clinical studies were conducted to characterise the PK of eflornithine/sulindac: 2 bioavailability/bioequivalence studies (CPP-P9-658 and CPP-P6-366), a dedicated renal impairment study of eflornithine (ELA-P4-466) and a pivotal phase 3 study (CPP-FAP-310).

**Bioanalytical methods**

All bioanalytical method validation reports, and associated data analysis reports, were assessed in the context of the EMA guideline on method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**).

*Bioanalytical Method Validation*

LC-MS/MS based methods for the determination of eflornithinein/ difluoromethylornithine (DFMO) sulindac, sulindac sulphide and sulindac sulfone in human plasma using Li heparin as an anticoagulant were validated.

**Table 3: Methods used in clinical pharmacology studies**

| Analyte | Clinical Study ID | Validated Range (ng/mL) |
|---|---|---|
| **Eflornithine/DFMO** | | |
| | CPP-P9-658 | |
| | ELA-P4-466 | 35 – 35000 |
| | CPP-P6-366 | |
| | FAP-310 | 50 - 100000 |
| **Sulindac** | | |
| | CPP-P9-658 | 30 - 15000 |
| | CPP-P6-366 | 30 - 15000 |
| | FAP-310 | 50 - 10000 |
| **Sulindac Sulfide** | | |
| | CPP-P9-658 | 10.0 - 8000 |
| | CPP-P6-366 | 10.0 - 8000 |
| | FAP-310 | 50 - 5000 |
| **Sulindac Sulfone** | | |
| | CPP-P9-658 | 10.0 - 8000 |
| | CPP-P6-366 | 10.0 - 8000 |
| | FAP-310 | 50 - 5000 |

Concentrations were calculated using peak area ratios and the linearity of the calibration curve was determined using a weighted ($1/x^2$) linear ($y=mx+b$) least squares regression analysis. Linear responses in the analyte and internal standard (IS) ratios were observed in spiked calibration standards (CS) and quality control (QC) samples, respectively, for each method. Bioanalytical method validation reports provide data pertaining to selectivity in the presence of concomitantly administered medications; lower limit of quantification (LLOQ); characterisation of potential matrix interference; intra- and inter-assay accuracy and precision; dilution integrity; carryover and analyte stability.

Back calculated CS were within ±20% of the nominal value at the LLOQ, and ±15% for all other concentration levels above the LLOQ, using a minimum of 6 non-zero concentration levels. Intra- and inter-assay precision (%CV) was acceptable for the QC sample concentrations presented (i.e. %CV for low, medium and high QC samples <15%, respectively). The intra- and inter-assay accuracy (percent relative error [%RE]) was within ±15% of the nominal values for low, medium and high QC samples were utilised, and within ±20% for the LLOQ.

*Bioanalytical Analysis of Samples*

During the analysis of participant samples, spiked CS and QC standards were extracted to permit the determination of the concentration of eflornithine/DFMO, sulindac, sulindac –sulfide and sulindac-sulfone, and their respective internal standards. Appropriate quality control (QC) samples allowed for the determination of method accuracy and precision during bioanalysis. Information pertaining to transportation, handling and storage of samples was also provided. Incurred sample reanalysis (ISR) was performed during assessment to ensure method reproducibility.

**Population PK analysis of eflornithine and sulindac**

### *Eflornithine model*

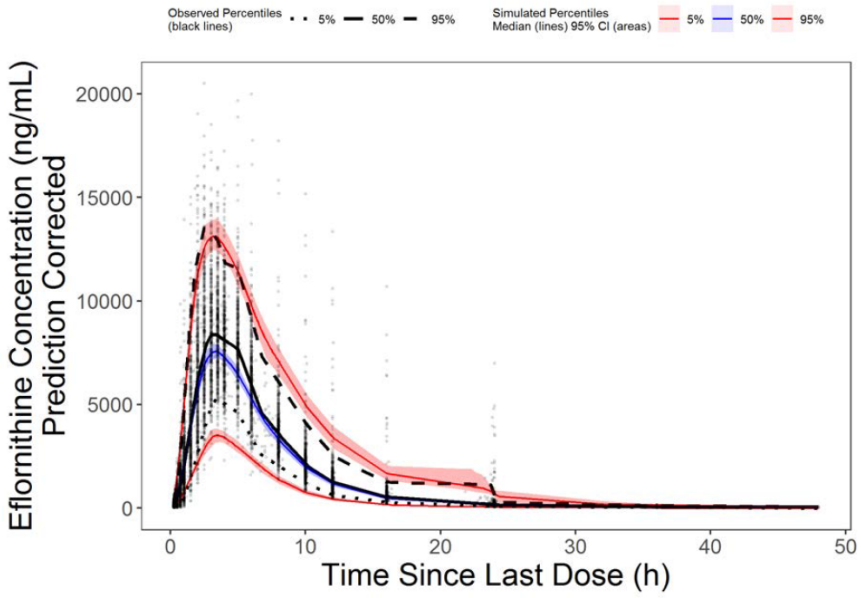
The eflornithine PK analysis dataset included 7830 measurable PK observations from 246 subjects in 3 Phase 1 studies CPP-P9-658, ELA-P4-466, and CPP-P6-366 and 1 Phase 3 study FAP-310. BLQ observations after administration of the first dose account for 8.4% of all observations.

The final model consisted of 2-compartments, with sequential zero and first order absorption. Covariates included in the final model were body weight on V, CRCL on CL, moderate renal impairment on CL, severe renal impairment on CL, moderate or severe renal impairment on Ka, and FAP subject on V and Ka. The parameter estimates for the final population PK model are presented in Table 4. A prediction-corrected VPC for the final model is displayed in Figure 4.

**Table 4: Final model parameter estimates for Eflornithine PK**

| Parameters | Estimates | %RSE | 95% CI | Shrinkage (%) |
|---|---|---|---|---|
| CL (L/h) | 13.02 | 2.1 | 12.49 - 13.55 | - |
| CRCL on CL | 0.4797 | 13.4 | 0.3539 - 0.6056 | - |
| Severe renal impairment on CL | -0.4745 | 13.2 | -0.5975 - -0.3515 | - |
| Moderate renal impairment on CL | -0.2597 | 24.5 | -0.3843 - -0.135 | - |
| V (L) | 27.29 | 4.4 | 24.93 - 29.64 | - |
| Body weight on V | 1.047 | 9.3 | 0.8549 - 1.238 | - |
| FAP subject on V | 1.406 | 11.3 | 1.093 - 1.718 | - |
| Q (L) | 1.467 | 3.6 | 1.363 - 1.572 | - |
| VP (L/h) | 15.45 | 2.8 | 14.6 - 16.3 | - |
| TK0 (h) | 1.788 | 3.8 | 1.655 - 1.921 | - |
| Ka (1/h) | 0.355 | 3.1 | 0.3316 - 0.3745 | - |
| FAP subject on Ka | 1.722 | 15.1 | 1.213 - 2.23 | - |
| Moderate or severe renal impairment on Ka | -0.2952 | 33.6 | -0.4897 - -0.1006 | - |
| **Random effects** | **Estimates (%CV)** | **%RSE** | **95% CI** | **Shrinkage (%)** |
| IIV on CL | 22.6 | 4.3 | - | 6 |
| IIV on V | 26.5 | 9.1 | - | 23 |
| IIV on Q | 19.9 | 10.9 | - | 46 |
| IIV on VP | 38.6 | 6.2 | - | 14 |
| IIV on TK0 | 8.6 | 31.5 | - | 65 |
| **Residual error** | **Estimates** | **%RSE** | **95% CI** | **Shrinkage (%)** |
| Proportional error | 0.2989 | 0.5 | 0.2963 - 0.3016 | - |
| Additive | 0.001 FIX | - | - | - |

Source: sumo-refine004.txt, sumo-refine004-ci.txt, refine004.lst
CI=confidence interval; CL=clearance; CV=coefficient of variation; F=bioavailability; IIV=inter-individual variability; KA=absorption rate constant; Q=inter-compartmental clearance; RSE=relative standard error; V=central volume of distribution; VP=peripheral volume of distribution, TK0= duration of zero-order absorption process



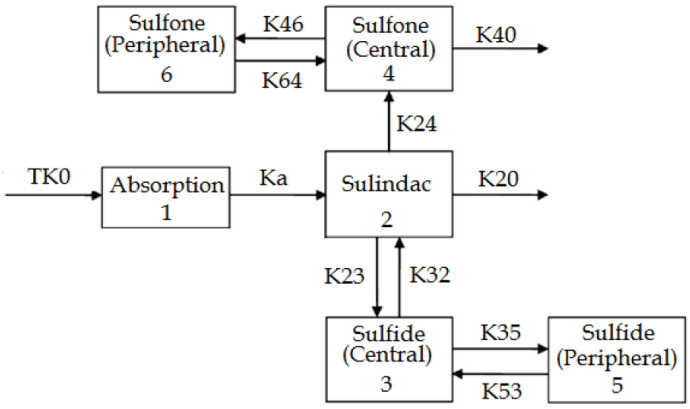

Source: EFL-vpc.R
Notes: Gray dots are observed data points; black solid line is the observed median; black dashed lines are observed p5 and p95. The pink area is the 95% prediction interval (PI) of the simulated median, and blue areas are the 95% PI of the simulated p5 and p95.

**Figure 4: Prediction-corrected VPC for eflornithine**

### *Sulindac model*

The sulindac PK analysis dataset included 22154 measurable PK observations from 205 subjects in 3 Phase 1 studies CPP-P9-658, and CPP-P6-366 and 1 Phase 3 study FAP-310. BLQ observations after administration of the first dose account for 14% of all observations.

The final model for sulindac and its two metabolites (sulindac sulphide and sulindac sulfone) consisted of 6 compartments including a 1-compartment disposition model for sulindac and a 2-compartment disposition model to describe the behaviour of both metabolites Absorption was best described using a sequential zero and first order absorption model (Figure 5).




Abbreviations: Kn=rate constants between compartments; TK0= duration of zero-order absorption process.

**Figure 5: Structural PK model for sulindac**

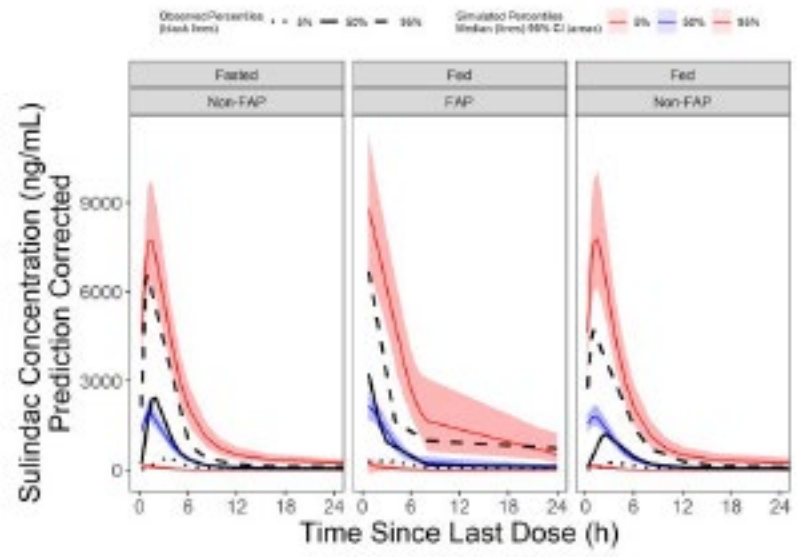
Covariate effects included in the final model were weight on V, FAP subject on Ka, and FED status on Ka and F. The parameter estimates for the final population PK model are presented in Table 6. Updated VPCs for each analyte in the final model are also displayed below.

**Table 5: Final model parameter estimates for sulindac PK**

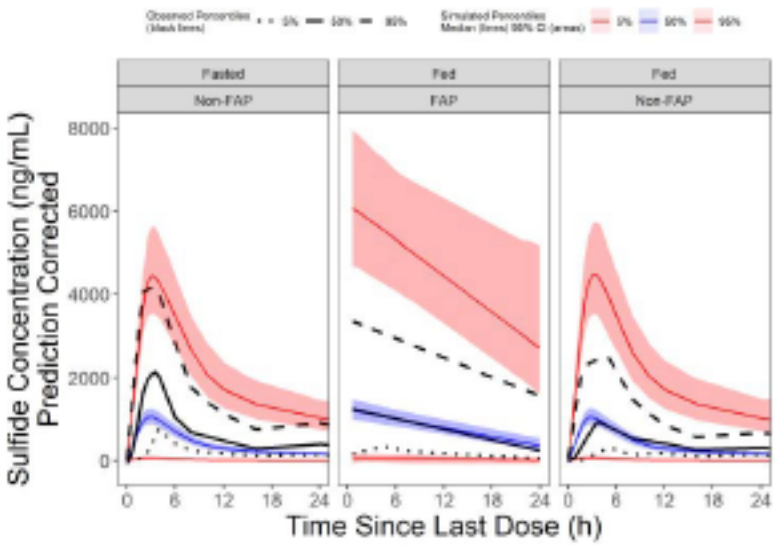
| Parameters | Estimates | %RSE | 95% CI | Shrinkage (%) |
|---|---|---|---|---|
| V (L) | 8.879 | 6.05 | 7.826 - 9.932 | - |
| Body weight on V | 0.7902 | 17.0 | 0.5266 - 1.054 | - |
| K23 (1/h) | 0.7791 | 0.4807 | 0.7717 - 0.7864 | - |
| K32 (1/h) | 0.4216 | 3.494 | 0.3927 - 0.4504 | - |
| K35 (1/h) | 0.5895 | 1.557 | 0.5715 - 0.6075 | - |
| K53 (1/h) | 0.1289 | 6.309 | 0.113 - 0.1449 | - |
| K24 (1/h) | 0.733 | 3.945 | 0.6763 - 0.7897 | - |
| K46 (1/h) | 1.585 | 2.975 | 1.492 - 1.677 | - |
| K64 (1/h) | 0.2062 | 2.106 | 0.1977 - 0.2147 | - |
| K12 (1/h) | 0.3652 | 0.7857 | 0.3595 - 0.3708 | - |
| Fasted effect on K12 | 0.6567 | 1.0 | 0.6433 - 0.6701 | - |
| FAP status effect on K12 | 0.6252 | 9.4 | 0.5095 - 0.7409 | - |
| K20 (1/h) | 0.9883 | 11.27 | 0.7700 - 1.206 | - |
| K40 (1/h) | 0.4568 | 3.583 | 0.4248 - 0.4889 | - |
| TK0 (h) | 0.6804 | 10.95 | 0.5345 - 0.8264 | - |
| F | 1 FIX | - | - | - |
| Fasted effect on F | 0.2085 | 2.06 | 0.2001 - 0.2169 | - |
| **Random effects** | **Estimates (%CV)** | **%RSE or correlation** | **95% CI** | **Shrinkage (%)** |
| IIV on V | 53.6 | 7.36 | - | 14 |
| ηV-ηK20 correlation | -0.8456 | - | - | - |
| IIV on K20 | 85.7 | 8.9 | - | 16 |
| IIV on K32 | 33.3 | 7.654 | - | 13 |
| IIV on K53 | 43.9 | 8.785 | - | 30 |
| IIV on K24 | 39.0 | 6.497 | - | 11 |
| IIV on K40 | 25.9 | 9.721 | - | 21 |
| IIV on TK0 | 122.8 | 7.074 | - | 15 |
| **Residual error** | **Estimates** | **%RSE** | **95% CI** | **Shrinkage (%)** |
| Sulindac proportional error | 0.594 | 1.1 | 0.5813 - 0.6067 | - |
| Sulindac additive error | 0.0001 FIX | - | - | - |
| Sulfide proportional error | 0.5024 | 1.2 | 0.4910 - 0.5138 | - |
| Sulfide additive error | 15.34 | 5.0 | 13.82 - 16.86 | - |
| Sulfone proportional error | 0.3903 | 0.9 | 0.3830 - 0.3975 | - |
| Sulfone additive error | 19.93 | 4.1 | 18.34 - 21.52 | - |

Source: sumo-refsul01.txt, sumo-refsul01-ci.txt, refsul01.lst
Abbreviations: CI=confidence interval; CV=coefficient of variation; FAP=familial adenomatous polyposis, ALT=Alanine Aminotransferase, IIV=inter-individual variability; Kn=rate constants between compartments; TK0=duration of zero-order absorption; RSE=relative standard error; V=central volume of distribution

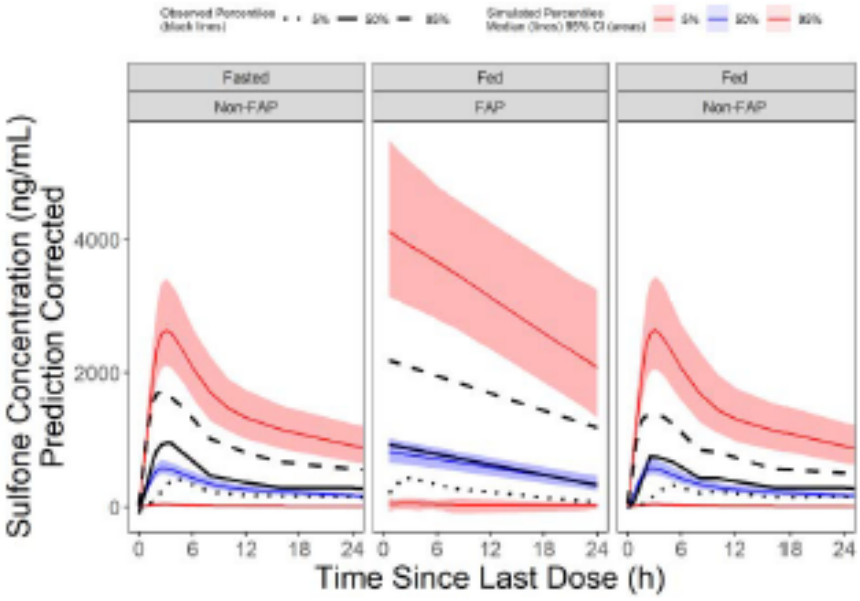
**Sulindac:**



**Sulindac Sulfide:**




**Sulindac Sulfone:**




## *Absorption*

- **Bioavailability**

Eflornithine

Clinical data indicate that 54-58% of orally administered eflornithine is absorbed (Haegele et al. 1981). After oral administration of the eflornithine/sulindac FDC to healthy subjects under fed conditions, median Tmax for eflornithine was 3.5 hours (range 2-5 hours) (Study CPP-P6-366).

Sulindac

Sulindac is about 90% absorbed after an oral tablet dose (Actavis May 2016). After oral administration of the eflornithine/sulindac FDC to healthy subjects under fed conditions, median Tmax for sulindac,

sulindac sulphide and sulindac sulfone were 2.5 hours (range 0.5-6 hours), 4.0 hours (range 1.5-10 hours) and 3.5 hours (range 1.5-16 hours) (Study CPP-P6-366).

- **Bioequivalence**

***Study CPP-P9-658***

This was a pilot study using a single centre, randomised, single dose, open-label, 4-period, 4-sequence, crossover design to assess a fixed co-formulated eflornithine/sulindac tablet relative to eflornithine and sulindac tablets co-administered in healthy subjects under fasted conditions. 12 healthy male or female subjects (M/F n=6/6) aged 18-60 years old were recruited and randomised to one of four treatment sequences.

- **Treatment-1 (co-formulated tablet):** a single 750/150 mg dose of Test-1 formulation (2 x 375/75 mg tablets)
- **Treatment 2 (individual eflornithine):** a single 750 mg dose of Test-2 formulation (3 x 250 mg tablets)
- **Treatment-3 (individual sulindac):** a single 150 mg dose of Reference (1 x 150 mg tablet)
- **Treatment-4 (co-administered eflornithine and sulindac):** a single 150 mg dose of Reference (1 x 150 mg tablet) and a single 750 mg dose of Test-2 (3 x 250 mg tablets) co-administered.

*Bioequivalence analysis results*

Eflornithine

**Summary of the Statistical Analysis of Eflornithine - Treatment-1 vs Treatment-2**

| PARAMETER | INTRA-SUBJECT C.V. (%) | GEOMETRIC LSMEANS * | | RATIO (%) | 90% CONFIDENCE LIMITS (%) | |
|---|---|---|---|---|---|---|
| | | Treatment-1 (n=12) | Treatment-2 (n=12) | | LOWER | UPPER |
| $C_{max}$ | 16.8 | 10430.9 | 10030.8 | 103.99 | 92.42 | 117.01 |
| $AUC_{0-T}$ | 13.5 | 69998.7 | 67701.4 | 103.39 | 94.03 | 113.69 |
| $AUC_{0-\infty}$ | 13.4 | 70395.4 | 68056.2 | 103.44 | 94.17 | 113.61 |

* units are ng/mL for $C_{max}$ and ng·h/mL for $AUC_{0-T}$ and $AUC_{0-\infty}$

**Summary of the Statistical Analysis of Eflornithine - Treatment-2 vs Treatment-4**

| PARAMETER | INTRA-SUBJECT C.V. (%) | GEOMETRIC LSMEANS * | | RATIO (%) | 90% CONFIDENCE LIMITS (%) | |
|---|---|---|---|---|---|---|
| | | Treatment-2 (n=12) | Treatment-4 (n=12) | | LOWER | UPPER |
| $C_{max}$ | 16.8 | 10030.8 | 9722.7 | 103.17 | 91.69 | 116.09 |
| $AUC_{0-T}$ | 13.5 | 67701.4 | 68916.4 | 98.24 | 89.34 | 108.02 |
| $AUC_{0-\infty}$ | 13.4 | 68056.2 | 69338.0 | 98.15 | 89.36 | 107.81 |

* units are ng/mL for $C_{max}$ and ng·h/mL for $AUC_{0-T}$ and $AUC_{0-\infty}$

**Summary of the Statistical Analysis of Eflornithine- Treatment-1 vs Treatment-4**

| PARAMETER | INTRA-SUBJECT C.V. (%) | GEOMETRIC LSMEANS * | | RATIO (%) | 90% CONFIDENCE LIMITS (%) | |
|---|---|---|---|---|---|---|
| | | Treatment-1 (n=12) | Treatment-4 (n=12) | | LOWER | UPPER |
| $C_{max}$ | 16.8 | 10430.9 | 9722.7 | 107.28 | 95.35 | 120.72 |
| $AUC_{0-T}$ | 13.5 | 69998.7 | 68916.4 | 101.57 | 92.37 | 111.68 |
| $AUC_{0-\infty}$ | 13.4 | 70395.4 | 69338.0 | 101.53 | 92.43 | 111.51 |

* units are ng/mL for $C_{max}$ and ng·h/mL for $AUC_{0-T}$ and $AUC_{0-\infty}$

Sulindac

**Summary of the Statistical Analysis of Sulindac - Treatment-1 vs Treatment-3**

| PARAMETER | INTRA-SUBJECT C.V. (%) | GEOMETRIC LSMEANS * | | RATIO (%) | 90% CONFIDENCE LIMITS (%) | |
|---|---|---|---|---|---|---|
| | | Treatment-1 (n=12)** | Treatment-3 (n=12)** | | LOWER | UPPER |
| $C_{max}$ | 24.6 | 4353.6 | 4888.5 | 89.06 | 75.04 | 105.69 |
| $AUC_{0-T}$ | 11.9 | 10746.4 | 11063.6 | 97.13 | 89.34 | 105.60 |
| $AUC_{0-\infty}$ | 13.6 | 12029.4 | 12743.6 | 94.40 | 82.27 | 108.30 |

* units are ng/mL for $C_{max}$ and ng·h/mL for $AUC_{0-T}$ and $AUC_{0-\infty}$
** n=7 for $AUC_{0-\infty}$

**Summary of the Statistical Analysis of Sulindac - Treatment-3 vs Treatment-4**

| PARAMETER | INTRA-SUBJECT C.V. (%) | GEOMETRIC LSMEANS * | | RATIO (%) | 90% CONFIDENCE LIMITS (%) | |
|---|---|---|---|---|---|---|
| | | Treatment-3 (n=12)** | Treatment-4 (n=12)*** | | LOWER | UPPER |
| $C_{max}$ | 24.6 | 4888.5 | 4704.2 | 103.92 | 87.56 | 123.32 |
| $AUC_{0-T}$ | 11.9 | 11063.6 | 10530.9 | 105.06 | 96.63 | 114.22 |
| $AUC_{0-\infty}$ | 13.6 | 12743.6 | 11834.3 | 107.68 | 93.31 | 124.27 |

* units are ng/mL for $C_{max}$ and ng·h/mL for $AUC_{0-T}$ and $AUC_{0-\infty}$
** n=7 for $AUC_{0-\infty}$
*** n=8 for $AUC_{0-\infty}$

**Summary of the Statistical Analysis of Sulindac- Treatment-1 vs Treatment-4**

| PARAMETER | INTRA-SUBJECT C.V. (%) | GEOMETRIC LSMEANS * | | RATIO (%) | 90% CONFIDENCE LIMITS (%) | |
|---|---|---|---|---|---|---|
| | | Treatment-1 (n=12)** | Treatment-4 (n=12)*** | | LOWER | UPPER |
| $C_{max}$ | 24.6 | 4353.6 | 4704.2 | 92.55 | 77.98 | 109.83 |
| $AUC_{0-T}$ | 11.9 | 10746.4 | 10530.9 | 102.05 | 93.86 | 110.94 |
| $AUC_{0-\infty}$ | 13.6 | 12029.4 | 11834.3 | 101.65 | 88.09 | 117.30 |

* units are ng/mL for $C_{max}$ and ng·h/mL for $AUC_{0-T}$ and $AUC_{0-\infty}$
** n=7 for $AUC_{0-\infty}$
*** n=8 for $AUC_{0-\infty}$

Sulindac sulphide and sulfone

Bioequivalence criteria were met for both metabolites with Cmax, $AUC_{0-t}$, and $AUC_{0-\infty}$ within the acceptance range limits of 80.00% - 125.00%.

***Study CPP-P6-366 (pivotal bioequivalence and food effect study)***

The study was a single centre, phase I, randomised, single-dose, laboratory-blinded, 4-period, 4-sequence, crossover design. 92 healthy male or female subjects aged 18-60 years old were recruited and randomised to one of four treatment sequences.

- Treatment-1: A single eflornithine/sulindac 750/150 mg dose (2 x 375/75 mg FDC film-coated tablets) given under fed conditions.
- Treatment 2: A single eflornithine/sulindac 750/150 mg dose (2 x 375/75 mg FDC film-coated tablets) given under fasting conditions.
- Treatment-3: A single 150 mg dose of sulindac (1 x 150 mg tablet) and a single 750 mg dose of eflornithine (3 x 250 mg tablets) co-administered under fed conditions.
- Treatment-4: A single 150 mg dose of sulindac (1 x 150 mg tablet) and a single 750 mg dose of eflornithine (3 x 250 mg tablets) co-administered under fasting conditions

*Bioequivalence analysis results*

Eflornithine

***FDC vs co-administration bioequivalence under fed conditions***

| Parameter (Unit) | Global Intra-Subject C.V. (%) | Geometric LSmeans | | Ratio (%) | 90% Confidence Limits (%) | |
|---|---|---|---|---|---|---|
| | | Treatment-1 (n=87) | Treatment-3 (n=87) | | Lower | Upper |
| $C_{max}$ (ng/mL) | 16.3 | 9435.5 | 9269.7 | 101.79 | 97.72 | 106.02 |
| $AUC_{0-T}$ (ng·h/mL) | 10.7 | 59389.0 | 58987.1 | 100.68 | 98.03 | 103.41 |
| $AUC_{0-\infty}$ (ng·h/mL) | 10.6 | 59871.8 | 59489.4 | 100.64 | 98.01 | 103.34 |

Treatment 1: Co-formulation fed conditions
Treatment 3: Co-administered fed conditions

***FDC vs co-administration bioequivalence under fasting conditions***

| Parameter (Unit) | Global Intra-Subject C.V. (%) | Geometric LSmeans | | Ratio (%) | 90% Confidence Limits (%) | |
|---|---|---|---|---|---|---|
| | | Treatment-2 (n=88) | Treatment-4 (n=87) | | Lower | Upper |
| $C_{max}$ (ng/mL) | 16.3 | 9801.0 | 9731.0 | 100.72 | 96.71 | 104.89 |
| $AUC_{0-T}$ (ng·h/mL) | 10.7 | 64951.7 | 66192.4 | 98.13 | 95.55 | 100.77 |
| $AUC_{0-\infty}$ (ng·h/mL) | 10.6 | 65419.9 | 66636.3 | 98.17 | 95.62 | 100.80 |

Treatment 2: Co-formulation fast conditions
Treatment 4: Co-administered fast conditions

Sulindac

***FDC vs co-administration bioequivalence under fed conditions***

| Parameter (Unit) | Global Intra-Subject C.V. (%) | Geometric LSmeans | | Ratio (%) | 90% Confidence Limits (%) | |
|---|---|---|---|---|---|---|
| | | Treatment-1 (n=87)[a] | Treatment-3 (n=87)[b] | | Lower | Upper |
| $C_{max}$ (ng/mL) | 42.4 | 2467.6 | 2123.6 | 116.20 | 104.92 | 128.70 |
| $AUC_{0-T}$ (ng·h/mL) | 14.1 | 8320.3 | 7839.9 | 106.13 | 102.46 | 109.92 |
| $AUC_{0-\infty}$ (ng·h/mL) | 14.5 | 8441.2 | 7866.1 | 107.31 | 102.91 | 111.91 |

[a] n=63 for $AUC_{0-\infty}$
[b] n=78 for $AUC_{0-\infty}$
Treatment 1: Co-formulation fed conditions
Treatment 3: Co-administered fed conditions

***FDC vs co-administration bioequivalence under fasting conditions***

| Parameter (Unit) | Global Intra-Subject C.V. (%) | Geometric LSmeans | | Ratio (%) | 90% Confidence Limits (%) | |
|---|---|---|---|---|---|---|
| | | Treatment-2 (n=88)[a] | Treatment-4 (n=87)[b] | | Lower | Upper |
| $C_{max}$ (ng/mL) | 42.4 | 3684.8 | 3989.6 | 92.36 | 83.43 | 102.25 |
| $AUC_{0-T}$ (ng·h/mL) | 14.1 | 10422.0 | 10400.7 | 100.21 | 96.76 | 103.77 |
| $AUC_{0-\infty}$ (ng·h/mL) | 14.5 | 10738.2 | 10624.3 | 101.07 | 96.78 | 105.55 |

[a] n=64 for $AUC_{0-\infty}$
[b] n=68 for $AUC_{0-\infty}$
Treatment 2: Co-formulation fast conditions
Treatment 4: Co-administered fast conditions

Sulindac sulphide and sulfone

Bioequivalence criteria were met for both metabolites with Cmax, $AUC_{0-t}$, and $AUC_{0-\infty}$ within the acceptance range limits of 80.00% - 125.00%.

**Influence of food**

**Study CPP-P6-366**

Eflornithine

**Food effect**

| Parameter (Unit) | Global Intra-Subject C.V. (%) | Geometric LSmeans | | Ratio (%) | 90% Confidence Limits (%) | |
|---|---|---|---|---|---|---|
| | | Treatment-1 (n=87) | Treatment-2 (n=88) | | Lower | Upper |
| $C_{max}$ (ng/mL) | 16.3 | 9435.5 | 9801.0 | 96.27 | 92.44 | 100.26 |
| $AUC_{0-T}$ (ng·h/mL) | 10.7 | 59389.0 | 64951.7 | 91.44 | 89.03 | 93.90 |
| $AUC_{0-\infty}$ (ng·h/mL) | 10.6 | 59871.8 | 65419.9 | 91.52 | 89.14 | 93.97 |

Treatment 1: Co-formulation fed conditions
Treatment 2: Co-formulation fast conditions

Sulindac

**Food effect**

| Parameter (Unit) | Global Intra-Subject C.V. (%) | Geometric LSmeans | | Ratio (%) | 90% Confidence Limits (%) | |
|---|---|---|---|---|---|---|
| | | Treatment-1 (n=87)[a] | Treatment-2 (n=88)[b] | | Lower | Upper |
| $C_{max}$ (ng/mL) | 42.4 | 2467.6 | 3684.8 | 66.97 | 60.48 | 74.14 |
| $AUC_{0-T}$ (ng·h/mL) | 14.1 | 8320.3 | 10422.0 | 79.83 | 77.09 | 82.68 |
| $AUC_{0-\infty}$ (ng·h/mL) | 14.5 | 8441.2 | 10738.2 | 78.61 | 75.21 | 82.16 |

[a] n=63 for $AUC_{0-\infty}$
[b] n=64 for $AUC_{0-\infty}$
Treatment 1: Co-formulation fed conditions
Treatment 2: Co-formulation fast conditions

Sulindac sulphide and sulfone

An effect of food was also demonstrated for sulindac sulphide, with decreased exposure in terms of AUC and Cmax of 26% and 45%, respectively, in the fed relative to fasting state. No effect of food was evident for sulindac sulfone exposure with CIs for both AUC and Cmax within the acceptance criteria.

## *Distribution*

Eflornithine

After oral administration of the eflornithine/sulindac FDC to healthy subjects under fed conditions, the mean apparent volume of distribution (V/F) for eflornithine was 94.1 L, based on non-compartmental

analysis (Study CPP-P6-366). In the population PK analysis, the volume of distribution for eflornithine was estimated to 43.4 L (Vc + Vp) for a non-FAP subject weighing 75 kg. In FAP subjects, Vc was increased by 141%.

Clinical data reported in the literature show that eflornithine does not bind significantly to human plasma proteins (Haegele et al. 1981).

Sulindac

After oral administration of the eflornithine/sulindac FDC to healthy subjects under fed conditions, the mean apparent volume of distribution (V/F) for sulindac was 170.2 L, based on non-compartmental analysis (Study CPP-P6-366). In the population PK analysis, the volume of distribution for sulindac, was estimated to 8.9 L for a subject weighing 75 kg.

Sulindac and its sulfide and sulfone metabolites are extensively bound.

## *Elimination*

Eflornithine

After oral administration of the eflornithine/sulindac FDC to healthy subjects under fed conditions, the mean elimination half-life for eflornithine was 5.15 hours and apparent clearance was 12.8 L/h, based on non-compartmental analysis (Study CPP-P6-366). In the population PK analysis, clearance of eflornithine was estimated to 13.0 L/h for a typical subject weighing 75 kg.

Sulindac

In Study CPP-P6-366, after oral administration of the eflornithine/sulindac FDC to healthy subjects under fed conditions, the mean elimination half-life for sulindac was 7.28 hours and apparent clearance was 20.2 L/h, based on non-compartmental analysis. The mean elimination half-lives of sulindac sulphide and sulindac sulfone were 15.3 and 17.2 hours, respectively.

In the population PK analysis, apparent clearance of sulindac is calculated to be 8.8 L/h (V/F x Ke) for a typical subject weighing 75 kg.

- **Excretion**

Clinical data indicate that 86% of absorbed eflornithine is excreted in the urine unchanged (Haegele et al. 1981). Less than 1% of the dose is eliminated in the bile.

For sulindac, the primary route of excretion in man is via the urine as both sulindac and its sulfone metabolite (free and glucuronide conjugates). Approximately 50% of the administered dose 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 faeces, primarily as the sulfone and sulfide metabolites (Actavis May 2016).

- **Metabolism**

Data from published studies indicate that eflornithine is not extensively metabolised (Marion-Merrell Dow, 1987). The non-clinical study CP101-004, using mixed human hepatocytes, did not identify any metabolites.

Following absorption, sulindac undergoes two major biotransformations; reversible reduction to the sulfide metabolite, and irreversible oxidation to the sulfone metabolite. Sulindac sulphide has anti-inflammatory properties and sulindac sulfone has anti-proliferative activity. Sulindac and sulindac sulfone undergo extensive enterohepatic circulation compared to the sulindac sulfide.

- **Interconversion**

No reversible metabolism has been reported for eflornithine. Therefore, interconversion was not discussed for this compound.

The interconversion between sulindac and its sulfide metabolite is considered to have a favourable effect on PK, PD and safety. The interconversion allows:

- on one hand to increase the residence time of the active moiety (sulfide) in the systemic circulation by excretion and subsequent reabsorption of the prodrug sulindac in the gut and then re-conversion to the active sulfide.
- on the other hand, the exposure of the gastrointestinal mucosa to sulindac sulfide is also reduced as the enterohepatic recirculation is achieved predominantly by sulindac and thus potential gastro-intestinal intolerance due to the active sulfide is limited.

- **Consequences of genetic polymorphism**

No data is necessary for eflornithine as it is not extensively metabolised.

Genetic polymorphism has been reported for some of the enzymes involved in sulindac metabolism. However, the impact of the polymorphisms of these enzymes, such as CYP1A2, CYP3A4 or FMO3, does not seem to be clinically relevant contrary to other enzymes such as CYP2D6. Moreover, sulindac is metabolised to its two main metabolites (sulfide and sulfone) by multiple pathways, CYPs and non-CYPs, so the impact of the reduced activity of one enzyme due to genetic polymorphism should be limited thanks to compensatory mechanisms via other metabolic pathways.

## *Dose proportionality and time dependencies*

Based on data from published studies, eflornithine exhibits approximately dose proportional PK over a wide range of doses. All studies performed with Flynpovi used the same dose of sulindac and no data on dose proportionality of sulindac is described in the literature, consequently no data on dose proportionality can be included in the SmPC.

No accumulation data after oral administration is available in the literature for eflornithine. The accumulation ratio of eflornithine predicted from terminal elimination constant (ke) and dosing interval (Tau=24 hours) is very close to 1 (1.04) indicating that very low accumulation is expected for eflornithine at steady-state. Sulindac extent of accumulation is described in Davies et al. 1997 with accumulation ratio ranging from 1.1 to 1.3, in line with the accumulation ratio predicted from terminal elimination constant (ke) obtained from single-dose data and dosing interval (Tau=24 hours).

Moreover, in both cases, no time dependence is accounted in the population PK model of eflornithine, with no change in clearance over time, indicating that neither of the two compounds has a time-dependent PK.

## *Intra- and inter-individual variability*

In the pivotal bioequivalence study (CPP-P6-366), global intra-individual variability of eflornithine was reported to be 16.3% and 10.6% for Cmax and AUC0-∞, respectively. For sulindac, global intra-individual variability was reported to be 42.4% and 14.5%, for Cmax and AUC0-∞, respectively.

In the population PK analysis, inter-individual variability of eflornithine on clearance and volume of the central compartment was 22.6% and 26.5%, respectively. Inter-individual variability of sulindac on elimination rate constant and volume of the central compartment was 85.7% and 53.6%, respectively.

## *Pharmacokinetics in the target population*

A pharmacokinetic substudy was performed within the phase 3 clinical trial, FAP-310, at the scheduled month 3 study visit, in all consenting participants.

Participants in study FAP-310, were randomised in equal proportions to receive, in a blinded manner, one of three study treatments for the entire study period:

1) CS: CPP-1X (3 x 250 mg tablets) + sulindac (1 x 150 mg tablet)

2) SP: Placebo (3 x 0 mg tablets) + sulindac (1 x 150 mg tablet)

3) CP: CPP-1X (3 x 250 mg tablets) + sulindac placebo (1 x 0 mg tablet).

Tablets were administered once daily with food.

The steady-state PK parameters for each analyte are provided in Table 6.

**Table 6: Summary of PK parameters, in the ITT group**

| Analyte | Parameter | N | Mean | SD | CV | Min | Max |
|---|---|---|---|---|---|---|---|
| Eflornithine | AUClast (ng*hr/mL) | 103 | 41254.4 | 12572.5 | 30.5 | 13822.6 | 73469.7 |
| | Cmax(ng/mL) | 103 | 7530.1 | 2605.3 | 34.6 | 2312.9 | 15577.8 |
| | Clast (ngmL) | 103 | 4148.2 | 1551.7 | 37.4 | 1432.5 | 8352.7 |
| | Tmax (hr) | 103 | 3.4 | 1.3 | 37.1 | 2.0 | 8.0 |
| | Tlast (hr) | 103 | 8.0 | 0.0 | 0.0 | 8.0 | 8.0 |
| Sulindac | AUClast (ng*hr/mL) | 100 | 9846.3 | 4362.8 | 44.3 | 1913.9 | 26259.4 |
| | Cmax(ng/mL) | 100 | 3518.4 | 2101.7 | 59.7 | 338.5 | 12668.3 |
| | Clast (ngmL) | 100 | 495.8 | 343.5 | 69.3 | 61.6 | 1465.8 |
| | Tmax (hr) | 100 | 1.6 | 1.5 | 92.8 | 0.0 | 8.0 |
| | Tlast (hr) | 100 | 8.0 | 0.4 | 5.0 | 4.0 | 8.0 |
| Sulindac Sulfide | AUClast (ng*hr/mL) | 100 | 10128.2 | 6796.2 | 67.1 | 1312.4 | 40636.8 |
| | Cmax(ng/mL) | 100 | 1816.9 | 1054.3 | 58.0 | 199.8 | 5900.4 |
| | Clast (ngmL) | 100 | 1092.1 | 812.1 | 74.4 | 177.8 | 4960.1 |
| | Tmax (hr) | 100 | 3.5 | 2.6 | 75.0 | 0.0 | 8.0 |
| | Tlast (hr) | 100 | 8.0 | 0.4 | 5.0 | 4.0 | 8.0 |
| Sulindac Sulfone | AUClast (ng*hr/mL) | 100 | 7686.5 | 4310.2 | 56.1 | 1600.3 | 23687.5 |
| | Cmax(ng/mL) | 100 | 1292.8 | 691.0 | 53.5 | 340.6 | 4118.6 |
| | Clast (ngmL) | 100 | 879.4 | 581.7 | 66.1 | 198.9 | 3718.0 |
| | Tmax (hr) | 100 | 3.4 | 2.4 | 70.5 | 1.0 | 8.0 |
| | Tlast (hr) | 100 | 8.0 | 0.4 | 5.0 | 4.0 | 8.0 |
| Source: Datalisting - Table 13: Pharmacokinetic Observations and Parameters ITT Population | | | | | | | |

A comparison of plasma analyte concentrations by treatment group is presented in Figure 6. These show similar profiles between treatment groups with overlapping 90% confidence intervals. There were no significant differences in Cmax, AUC or Tmax between the two formulation groups.

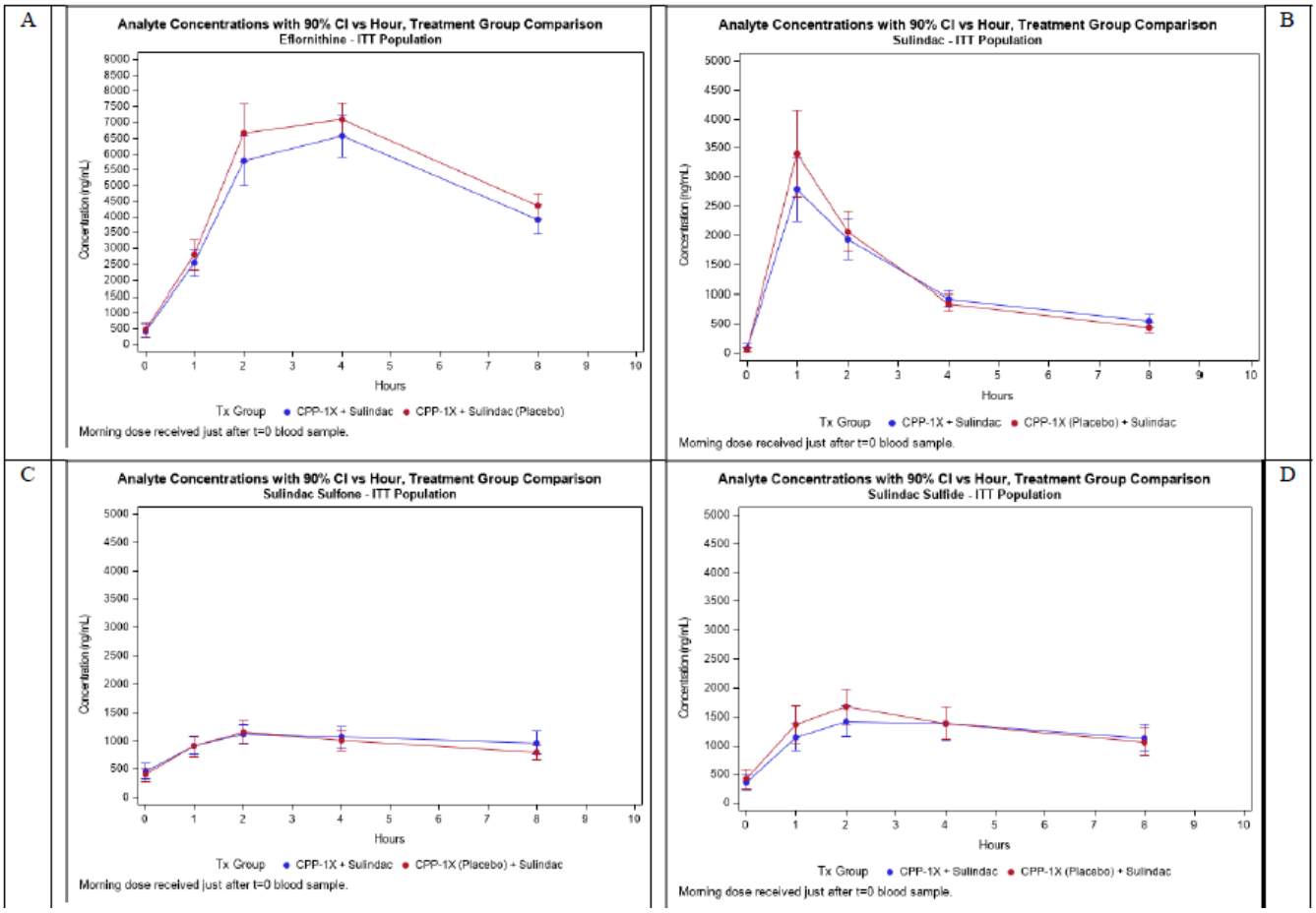



**Figure 6: Eflornithine, sulindac, sulindac sulphide, sulindac sulfone concentrations vs time by treatment group**

There were no significant differences between plasma analyte concentrations at any timepoint when comparing the disease strata of the subjects: duodenal polyposis, pre-colectomy, and rectal/pouch polyposis.

For the analytes eflornithine and sulindac, there were no significant differences in PK parameters (Cmax, AUC, Clast, Tmax) between patients with an intact colon and patients that had undergone an FAP disease related surgical intervention. For the analytes sulindac sulfone and sulindac sulphide, there were significant differences between the colon and no colon groups, with exposures of each metabolite being lower in patients with no colon compared to those with a colon.

**Table 7: Sulindac sulfone and sulindac sulfide PK observations for the subjects in FAP-310 based upon the presence or absence of a colon**

| | Colon (n=22) | No Colon (n=78) | p-value |
|---|---|---|---|
| **Sulindac Sulfide** | | | |
| AUClast (ng*hr/mL) Mean (SD) | 13702 (8273.6) | 9120.2 (6003.2) | 0.0035 |
| Cmax (ng/mL) Mean (SD) | 2326.9 (1198.3) | 1673.0 (970.8) | 0.0099 |
| Clast (ng/mL) Mean (SD) | 1400.2 (1017.4) | 1005.2 (728.6) | 0.0249 |
| **Sulindac Sulfone** | | | |
| AUClast (ng*hr/mL) Mean (SD) | 8788.5 (3454.6) | 7375.7 (4492.9) | 0.0423 |
| Cmax (ng/mL) Mean (SD) | 1489.9 (556.7) | 1237.2 (717.7) | 0.0389 |
| Tmax (ng/mL) Mean (SD) | 2.4 (1.6) | 3.6 (2.5) | 0.0254 |

Source: Datalisting -
Table 15: Pharmacokinetic Observations and Parameters Intact Colon Group ITT Population
Table 16: Pharmacokinetic Observations and Parameters No Colon Group ITT Population
Table 20: Statistics for Pharmacokinetic Parameters Observation: Intact Colon vs No Colon Groups ITT Population

## *Special populations*

- **Impaired renal function**

Study ELA-P4-466

This was a phase 1, multicentre, open-label, parallel-group adaptive single-dose study of oral eflornithine in adult subjects with normal and impaired renal function. 8 subjects, matched for gender, age and weight, were enrolled per renal function group: normal renal function (eGFR ≥90 mL/min/1.73 $m^2$), mild (eGFR 60-89 mL/min/1.73 $m^2$), moderate (eGFR 30-59 mL/min/1.73 $m^2$) and severe renal impairment (eGFR ≤29mL/min/1.73 $m^2$). All subjects received a single dose of 750 mg eflornithine in the fasted state.

Results of the pairwise ANOVA analysis are presented in Table 8. These show significant increases in peak and extent of exposure in subjects with moderate and severe renal impairment, but not in subjects with mild renal impairment. In subjects with moderate renal impairment, Cmax and AUC were increased by approximately 1.3-fold and 2-fold, respectively. In subjects with severe renal impairment, Cmax and AUC were increased by approximately 1.8-fold and 3-4-fold, respectively.

**Table 8: Pairwise comparisons of geometric least squares means from ANOVA**

| Parameters | Group | Geometric LSmeans[a] | Comparison | Adjusted p-value | Ratio (%) | 90% Confidence Limits (%) | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower | Upper |
| $C_{max}$ | Normal (n=8)<br>Mild (n=8)<br>Moderate (n=8)<br>Severe (n=8) | 6830.0<br>9025.8<br>9173.1<br>12315.8 | Mild vs Normal | 0.1096 | 132.15 | 99.46 | 175.59 |
| | | | Moderate vs Normal | 0.0139 | 134.31 | 108.23 | 166.66 |
| | | | Severe vs Normal | 0.0074 | 180.32 | 120.85 | 269.04 |
| | | | Mild vs Moderate | 0.9989 | 98.39 | 75.24 | 128.68 |
| | | | Mild vs Severe | 0.3263 | 73.29 | 47.64 | 112.74 |
| | | | Moderate vs Severe | 0.2860 | 74.48 | 50.48 | 109.90 |
| $AUC_{0-T}$ | Normal (n=8)<br>Mild (n=8)<br>Moderate (n=8)<br>Severe (n=8) | 52245.3<br>62212.8<br>100980.3<br>164815.7 | Mild vs Normal | 0.3348 | 119.08 | 93.26 | 152.05 |
| | | | Moderate vs Normal | <0.0001 | 193.28 | 149.23 | 250.33 |
| | | | Severe vs Normal | <0.0001 | 315.47 | 216.45 | 459.78 |
| | | | Mild vs Moderate | 0.0027 | 61.61 | 45.84 | 82.81 |
| | | | Mild vs Severe | <0.0001 | 37.75 | 25.23 | 56.48 |
| | | | Moderate vs Severe | 0.0377 | 61.27 | 40.59 | 92.49 |
| $AUC_{0-\infty}$ | Normal (n=8)<br>Mild (n=8)<br>Moderate (n=8)<br>Severe (n=8) | 53131.9<br>63089.9<br>112389.6<br>208464.8 | Mild vs Normal | 0.3507 | 118.74 | 92.94 | 151.70 |
| | | | Moderate vs Normal | <0.0001 | 211.53 | 155.97 | 286.88 |
| | | | Severe vs Normal | <0.0001 | 392.35 | 259.54 | 593.14 |
| | | | Mild vs Moderate | 0.0017 | 56.14 | 40.06 | 78.66 |
| | | | Mild vs Severe | <0.0001 | 30.26 | 19.53 | 46.89 |
| | | | Moderate vs Severe | 0.0199 | 53.91 | 33.57 | 86.60 |

Population PK analysis

The popPK model found both CRCL and moderate or severe renal impairment to be significant covariates. The effect of each covariate on eflornithine clearance (CL), the total effect on CL (effect of both CRCL and moderate or severe renal impairment category), and the total effect on AUC relative to a healthy volunteer were thus derived (Table 9).

**Table 9: Total effect of renal impairment (CRCL and moderate or severe renal impairment category) on eflornithine PK parameters**

| Renal Category | Original classification | Total effect on eflornithine Clearance | | | Total effect on eflornithine AUC | | |
|---|---|---|---|---|---|---|---|
| | | CI 5% | median | CI 95% | CI 5% | median | CI 95% |
| Normal | 216 | 93% | 100% | 107% | 107% | 100% | 93% |
| Mild | 8 | 77% | 85% | 93% | 123% | 115% | 107% |
| Moderate | 8 | 34% | 49% | 66% | 166% | 151% | 134% |
| Severe | 8 | 16% | 25% | 36% | 184% | 175% | 164% |

Renal function was not identified as a significant covariate for sulindac. Sulindac is contraindicated in subjects with severe renal impairment (see section 4.3 of the SmPC). There are no data available on sulindac in subjects with moderate renal impairment.

- **Impaired hepatic function**

No studies were conducted.

Sulindac is contraindicated in severe hepatic impairment (see section 4.3 of the SmPC). Limited data are available in patients with mild or moderate hepatic impairment but, based on data for sulindac (Juhl et al. 1983) and knowing that eflornithine is poorly metabolised and mostly excreted unchanged in urine, subjects with mild and moderate hepatic impairment could receive Flynpovi at regular dose with appropriate monitoring of their hepatic function.

- **Gender**

Sex was not identified as a significant covariate in the popPK analyses.

- **Race**

As more than 87% of subjects in the studies performed were White, it was not possible to determine race-related differences in PK of eflornithine or sulindac.

- **Weight**

The population PK model for eflornithine included body weight effect on volume but not on clearance. Simulated eflornithine profiles for a typical subject weighing either 45 or 135 kg have Cmax of 10608 ng/mL and 5051 ng/mL, respectively with identical steady state AUCs of 59055 ng*hr/mL. Simulated Cmax is in line with observed Cmax for subjects with similar weights.

Rate constants were modelled in the sulindac model. Since CL is derived as CL = K20*V*(WTcov), CL and body weight are directly proportional. An increased V due to higher body weight also results in a higher CL. Simulated sulindac profiles for a typical subject weighing either 45 or 135 kg have Cmax of 3974 ng/mL and 1668 ng/mL, respectively, and steady state AUCs of 14777 ng*hr/mL and 6204 ng*hr/mL, respectively. Simulated Cmax is in line with observed Cmax for subjects with similar weights.

To evaluate if weight played a role in the efficacy of sulindac administered either as a single agent or in the combination, efficacy endpoints of subjects weighing >135 kg in the CPP FAP-310 and the PSCA trials were assessed. None of the 5 subjects treated with eflornithine + sulindac that weighed ≥ 135 kg had an FAP-related event (CPP FAP-310) or developed new adenomas (PSCA) versus 1 of 2 of the placebo subjects on the PSCA study.

In study CPP FAP-310, the safety in subjects that were at the extreme high and low weight ranges in the CPP FAP-310 study were evaluated. There were only three subjects that had a baseline weight of either ≤45 kg or ≥135 kg. One of these subjects (42.7 kg) came off the study due to an adverse event (peptic ulcer and decreased appetite), which was possibly/probably drug related.

- **Elderly**

The combination of eflornithine and sulindac, Flynpovi, has not been extensively evaluated in elderly (Table 10).

**Table 10: Summary of elderly populations treated with eflornithine or the combination of eflornithine and sulindac**

| | Trial Name | Age 65-74 (Older subject number /total number) | Age 75-84 (Older subject number /total number) | Age 85+ (Older subject number /total number) |
|---|---|---|---|---|
| # Subjects exposed to eflornithine/ sulindac combination | CPP FAP-310 | 1/56 | 0/56 | 0/56 |
| | PSCA | 54/188 | 10/188 | 0/188 |
| | CPP-P6-366 | 0/23 | 0/23 | 0/23 |
| | CPP-P9-658 | 0/12 | 0/12 | 0/12 |
| # Subjects exposed to eflornithine | ELA-P4-466 | 6/32 | 1/32 | 0/32 |
| | CPP FAP-310 | 4/56 | 0/56 | 0/56 |

In the dataset used for population PK analysis of eflornithine, 12 patients (5%) were older than 65 years. However, there was no effect of age (range 18-75-year-old) or age group (> 65-year-old) in the population PK models of eflornithine. As shown in the box plot below, eflornithine clearance values in

younger subjects (< 65-year-old) and elderly (> 65-year-old) with normal renal function or mild renal impairment were comparable whereas eflornithine clearance is decreased in elderly with moderate or severe renal impairment (Figure 7).

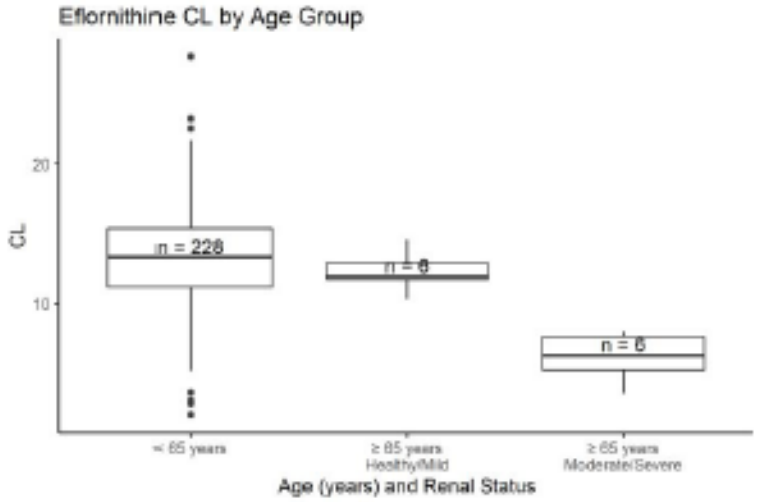



**Figure 7: Eflornithine clearance for subjects <65 year-old and for elderly subjects (>65 year-old) by renal function group**

The data do not justify to contra-indicate Flynpovi in elderly patients with normal renal function or mild renal impairment. These patients can be treated at the regular dose with appropriate monitoring of potential gastro-intestinal bleeding and renal function.

## *Pharmacokinetic interaction studies*

Eflornithine

*In vitro* results indicated that eflornithine is unlikely to be an inhibitor of cytochrome P450 isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) at concentrations up to 5500 µM, which is 138-fold higher than the anticipated clinical Cmax of 40 µM (Study 749N-1602).

*In vitro* results indicated that eflornithine is unlikely to be an inducer of CYP450 (CYP1A2, CYP2B6, and CYP3A4) and glucuronosyltransferase (UGT1A1, UGT1A3, UGT1A9, UGT2B7) enzymes at concentrations up to 5500 µM, which is 138-fold higher than the anticipated clinical Cmax of 40 µM (Study 749N-1603).

*In vitro* studies OPT-2017-159 and OPT-2018-012 showed that eflornithine is not an inhibitor of the transport mediated by OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, BCRP, P-gp or BSEP in the concentration range of 30 to 10,000 µM, with a 75-250X safety margin.

*In vitro* study OPT-2017-160 indicated that eflornithine, at doses up to 300 µM, is not a substrate of OAT1, OAT3, OCT1, OCT2, MATE1, MATE2-K, BCRP, P-gp or BSEP.

No clinical interaction studies were conducted for eflornithine.

Sulindac

The applicant submitted information from the authorised product information in the EU and US and literature data reflecting potential interactions between sulindac and probenecid, dimethyl sulfoxide, mifepristone, cardiac glycosides and zidovudine

## 2.4.3. Pharmacodynamics

The pharmacodynamic properties of eflornithine and sulindac were not specifically investigated in the current application. However, the pivotal phase 3 study in subjects with FAP (CPP-FAP-310) included a urine polyamine analysis and a pharmacogenetic analysis.

### *Mechanism of action*

Eflornithine, an antiproliferative agent, is an enzyme-activated, irreversible inhibitor of ornithine decarboxylase (ODC), an essential enzyme in the polyamine synthesis pathway. Mechanistic and translational studies in humans indicate that ODC enzyme activity is upregulated in the intestinal and colonic mucosa of patients with FAP.

Sulindac is a non-steroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic and antipyretic activities. In addition to these properties, it has been shown to be an antitumor agent. Based on both genetic and pharmacological studies, it is suggested that the antitumor effects are mediated, at least in part, through inhibition of cyclooxygenases (COX).

The pharmacological rationale for the combination of eflornithine and sulindac in patients with FAP is based on the complementary pharmacological activities of these compounds to reduce cellular polyamine levels: eflornithine affects polyamine synthesis and sulindac affects polyamine catabolism and cellular export. It is expected that the resulting reduction of polyamines will delay the progression and/or number of FAP-related events.

### *Primary and Secondary pharmacology*

Study CPP-FAP-310: Urine Polyamine Analysis

In the CPP-FAP-310 Phase 3 study, subjects were randomised into 1 of 3 treatment groups in a 1:1:1 ratio (CPP-1X 750 mg + sulindac 150 mg [N=56]: CPP-1X placebo + sulindac 150 mg [N=58]: CPP-1X 750 mg + sulindac placebo [N=57]). Subjects received once-daily treatment with study drug for up to 48 months.

Secondary efficacy outcomes included an evaluation of the excretion of urinary polyamines ($N^8$-acetylspermidine, $N^1$-acetylspermidine, and decarboxylated SAM (DcAdoMet)). Additional analytes assessed included putrescine, thymidine, $N^1$, $N^{12}$-diacetylspermine, prostaglandin E2 (PGE2) and 12-decarbox-delta-12,14-prostaglandin J2 (15dPGJ2). Creatinine was used to normalise protein content between samples.

*$N^8$-acetylspermidine*

At 6 months, a statistically significant decrease in $N^8$-acetylspermidine from baseline was observed in subjects treated with CPP-X+Sulindac [mean (±SD) percent change was -13.3 (±15.8) %, p<0.0001] and subjects treated with CPP-X [-13.4 (±18.9) %, p<0.0001]. The mean percent change in subjects treated with Sulindac was -2.4 (±20.3) % (p=0.41). The difference in percent change from baseline was statistically significant between CPP-1X+Sulindac vs Sulindac (p<0.0001) and between CPP-1X vs Sulindac (p=0.0009). The difference between CPP-1X+Sulindac vs CPP-1X was not statistically significant (p=0.59).

*$N^1$-acetylspermidine*

At 6 months, a statistically significant decrease in $N^1$-acetylspermidine from baseline was observed in subjects treated with CPP-X+Sulindac [mean (±SD) percent change was -17.2 (±28.5) %, p=0.0001] and subjects treated with CPP-X [-11.3 (±34.2) %, p=0.0247]. The mean percent change in subjects

treated with Sulindac was +8.1 (±39.8) % (p=0.16). The difference in percent change from baseline was statistically significant between CPP-1X+Sulindac vs Sulindac (p<0.0001) and between CPP-1X vs Sulindac (p=0.0010). The difference between CPP-1X+Sulindac vs CPP-1X was not statistically significant (p=0.45).

*Decarboxylated SAM (DcAdoMet)*

At 6 months, a statistically significant increase in DcAdoMet from baseline was observed in subjects treated with CPP-X+Sulindac [mean (±SD) percent change was +45.9 (±78.9) %, p=0.0002] and subjects treated with CPP-X [+24.6 (±80.1) %, p=0.0369]. The mean percent change in subjects treated with Sulindac was +14.81 (±67.6) % (p=0.14). The difference in percent change from baseline was statistically significant between CPP-1X+Sulindac vs Sulindac (p=0.0009) and CPP-1X+Sulindac vs CPP-1X (p=0.0297), and not statistically significant between CPP-1X vs Sulindac (p=0.33).

*Additional analytes*

Changes from baseline were less pronounced for other polyamine export substrates putrescine and $N^1$,$N^{12}$-diacetylspermine and the prostaglandin PGE2. Changes from baseline were generally not significant for all the treatment groups except for $N^1$, $N^{12}$-diacetylspermine which increased significantly from baseline in the CPP-1X+Sulindac and CPP-1X alone treatment groups after 6 months of treatment.

**PD interactions**

***Eflornithine***

Myelosuppressive Agents

Intravenous and high dose eflornithine was associated with reversible myelosuppression. Eflornithine in combination with chemotherapy agents such as the combination of procarbazine, N-(20chloroethly)-N'-cyclohextyl-N-nirourea and vincristine (PCV) results in increased percentage of patients experiencing grade 3 and 4 thrombocytopenia compared to the PCV group alone(Levin et al. 2000). Additionally, increased thrombocytopenia was observed in patients treated with eflornithine who had received prior chemotherapy (Abeloff et al. 1984; Abeloff et al. 1986).

Hence caution should be used when eflornithine is used with drugs that cause myelosuppression or in patients with existing myelosuppression as a result of a haematological disease.

Ototoxic Agents

High dose systemic eflornithine has also been associated with reversible hearing loss. Also the combination of eflornithine with IFN-a2b showed increased hearing loss at 1000 and 2000 Hz but not at other frequencies tested (Croghan, Aickin, and Meyskens 1991). Therefore, hearing should be monitored with serial audiograms when eflornithine is used with drugs that cause hearing loss such as certain classes of chemotherapeutic agents.

***Sulindac***

No new information provided.

**Genetic differences in PD response**

Study CPP-FAP-310: Pharmacogenetic analysis

In the CPP-FAP-310 Phase 3 study, blood samples were collected from patients with FAP and a retrospective analysis was performed to assess the ornithine decarboxylase single nucleotide polymorphisms (ODC SNPs), ODC+316 and ODC+263.

In subjects receiving the combination of CPP-1X + sulindac, the presence of ODC+316 minor allele did not have much impact on time to an FAP-related event until after 42 months, where more events occurred compared to subjects with the major allele; however, this was not statistically significant (p>0.30). In subjects were treated with sulindac alone, the ODC+316 genotype had little effect of time to an FAP-related event (p>0.97). In subjects treated with CPP-1X alone, the presence of the ODC+316 major allele (GG) had a statistically significant impact on time to an FAP-related event. The time to event was delayed compared to the subjects with minor allele (either GA or GA+AA) (HR=0.35, p=0.0173 between GG vs GA; HR=0.33, p=0.0104 between GG vs GA+AA).

In terms of the risk for having an FAP-related event, the effect of genotype among the patients in the combination group was not statistically significant. The effect of genotype among the patients in CPP-1lX group was statistically significant; subjects with the major allele had lower risk than subjects with minor allele (HR=0.306; 95% CI 0.131 to 0.713).

For subjects treated with combination of CPP-1X+sulindac, the presence of the ODC+263 major allele (genotype GG), more subjects had an FAP-related event and the events occurred sooner compared to the presence of any minor allele (homozygous minor or heterozygous); however, the difference was not statistically significant. When subjects were treated with either sulindac or CPP-1X alone, the presence of the ODC+263 minor allele did not have an impact on time to an FAP-related event.

## 2.4.4. Discussion on clinical pharmacology

The overall clinical pharmacology development plan relies on a limited number of sponsor-conducted studies, together with data from the published literature.

**Pharmacokinetics**

***Bioanalytical methods***

*Quality Statements*

Certificates of analysis for reference standards were provided. A statement on GLP and GCP compliance, in addition to a quality assurance regarding adherence to the study protocols and SOPs were also provided.

*Method Validation*

In general, methods for the determination of eflornithine (BMR-1786) / DFMO (125113AHDD), sulindac, sulindac-sulfide and sulindac-sulfone (BMR-1803 and 125112AHDA), were precise, accurate, sensitive and selective over the validated range. There was no evidence of carryover, any significant matrix effect or interference with concomitantly administered drugs.

*Bioanalysis of Samples*

In general, the bioanalysis of clinical samples was acceptable. Each analytical run included appropriate QC samples, while the accuracy and precision of calibration standards, in addition to QC samples, were acceptable. ISR provided evidence of method reproducibility.

For study FAP-310, the duration of sample storage from first collection to last extraction was 1256 days. Plasma stability has currently been assessed through day 1083 for both eflornithine and sulindac. The applicant committed to provide these stability reports as well as those of additional testing once available.

***Population PK analyses***

Standard methods were generally used for model development and evaluation. The structural models for both eflornithine and sulindac were based on previously published models with modifications.

Eflornithine model

The final popPK model for eflornithine was a 2-compartment model with linear elimination and sequential zero and first order absorption. Covariate effects included in the final model were body weight on V/F, CRCL on CL/F, moderate renal impairment on CL/F, severe renal impairment on CL/F, moderate or severe renal impairment on Ka, and FAP subject on V/F and Ka.

The GOF plots for the final model showed some under-prediction of high concentrations. Further, the VPCs indicated that the model does not fully capture the observed median concentrations and overestimates inter-individual variability. The applicant refined the model following re-categorisation of renal impairment status but GOF plots and VPCs for the updated model were largely unchanged. Thus, the predictive ability of the model is not considered adequate and simulations based on the model cannot be considered reliable.

Sulindac model

The final popPK model for sulindac and 2 metabolites (sulindac sulfide and sulindac sulfone) was a 6-compartment model including a 1-compartment model for sulindac and a 2-compartment model for each metabolite, linear elimination of each analyte, and sequential zero and first order absorption. Covariate effects included in the final model were body weight on V, FED status on Ka and F, and FAP status on Ka.

The GOF plots for the final model for each analyte (sulindac, sulindac sulfide and sulindac sulfone) showed over-prediction of high concentrations and under-prediction of low concentrations. The applicant presented updated VPCs for the final sulindac model, where observed median concentrations for each analyte were predicted reasonably well over the dosing interval for FAP subject under fed conditions. The applicant acknowledged that IIV was over-predicted for concentrations associated with Cmax and consider this to be due to the large IIV on TK0 (123%), which was the only absorption related parameter with where IIV could be included.

***Absorption***

- ***Bioavailability***

Section 5.2 of the SmPC includes current data on the absorption properties, including time to reach peak concentrations, of eflornithine, sulindac, sulindac sulphide and sulindac sulfone following oral administration of the eflornithine/sulindac FDC under fed conditions.

- ***Bioequivalence and food effect***

Study CPP-P9-658

The applicant has submitted a pilot study CPP-P9-658 to assess a fixed co-formulated eflornithine/sulindac tablet relative to eflornithine and sulindac tablets co-administered in healthy subjects under fasted conditions. The design of the conducted study is in general in accordance with the Guideline on the investigation of Bioequivalence [Guideline CPMP/EWP/QWP/1401/98 Rev.1/ Corr].

Bioequivalence criteria were met for all eflornithine, sulindac sulphide and sulindac sulfone PK parameters in the co-formulated tablet vs individual- and co-administration analyses. However, the CIs for sulindac $C_{max}$ were lower in the individual (treatment 1 v 3) and co- administered (treatment 1 v 4) groups versus the co-formulated tablet group (lower bound of CI = 75 and 78 %, respectively). This was attributed to high intra-individual variation

Study CPP-P6-366

The applicant has submitted study CPP-P6-366 to assess the bioequivalence of sulindac and eflornithine in healthy subjects in both fed and fasted states when administered orally in the FDC product proposed for

marketing relative to co-administration as in the pivotal efficacy study (CPP-FAP-310). The design of the conducted study is in general in accordance with the Guideline on the investigation of Bioequivalence [Guideline CPMP/EWP/QWP/1401/98 Rev.1/ Corr].

As anticipated, there was an effect of food on sulindac exposure with FDC groups demonstrating lower exposure in terms of Cmax and AUC in the fed state. Although the number of subjects in the PK analysis set in this analysis was less than that outlined in the *a priori* power calculations this result is accepted based on previous knowledge of sulindac absorption.

The CI for all PK parameters in the FDC vs co-administration analyses were within the acceptance criteria for bioequivalence with the exception of Cmax for sulindac which was higher in the FDC group relative to the co-administered group in the fed state (higher bound of CI = 128%). The proposed posology for the FDC is after food. Therefore, it is possible that this finding may present a safety concern specifically in terms of potential GI toxicity.

The applicant argues that as the proposed dose is half the licenced dose, the small increase in Cmax is unlikely to represent a safety concern. While in general, this is a reasonable argument, it should be noted that this product is proposed for chronic administration in a new patient population and in the absence of mechanistic data on toxicity (e.g. GI toxicity), there are no data on which to base a safety assessment as to the relevance of this finding. Despite this, it is accepted that the deviation from the predefined confidence intervals is relatively small and that this is unlikely to represent a significant safety or efficacy concern.

***Distribution***

Section 5.2 of the SmPC includes current data on the distribution properties of eflornithine and sulindac.

***Elimination***

Section 5.2 of the SmPC includes current data on the clearance of eflornithine and sulindac, and the elimination half-lives of eflornithine, sulindac, sulindac sulphide and sulindac sulfone.

***Pharmacokinetics in target population***

A PK substudy was conducted in the pivotal phase 3 trial (FAP-310) in FAP subjects. PK parameters were determined at the month 3 scheduled visit after steady-state was achieved.

The applicant claims that the PK parameters from the current study are consistent with those from Study CPP-P6-366 (a single dose BE study in healthy subjects). This is not considered an appropriate comparison since it compares single-dose with steady-state parameters. In addition, visual inspection of the PK parameter values in each study clearly shows that they are not similar (see also Study CPP-P6-366).

***Special populations***

- ***Impaired renal function***

<u>Eflornithine</u>

Study ELA-P4-466 was a single-dose study of oral eflornithine in subjects with normal and impaired renal function. The design of the study is generally acceptable.

The results showed peak (Cmax) and extent of exposure (AUCs) were significantly increased by approximately 1.8-fold and 3 to 4-fold, respectively, in subjects with severe renal impairment.

Cmax and AUC were also significantly increased by approximately 1.3-fold and 2-fold, respectively, in subjects with moderate renal impairment.

In the present study, BSA-normalised eGFR (mL/min/1.73 $m^2$) was used to estimate renal function in study subjects. In line with the EMA guideline on evaluation of PK in renal impairment (EMEA/CHMP/83874/2014), the applicant recalculated eGFR to the absolute eGFR in mL/min in study subjects, which resulted in the re-categorisation of subjects in terms of renal function. The applicant did not then re-analyse the data with the new categorisation. Instead, the applicant used the updated population PK model to evaluate the impact of renal function on eflornithine PK.

The applicant has proposed that patients with moderate or severe renal impairment should not be treated with Flynpovi, which is endorsed. The applicant has included moderate renal impairment as a contraindication in section 4.3 of the SmPC, together with severe renal impairment. This has also been reflected in section 4.2.

Sulindac

The lack of a dedicated study of sulindac in subjects with renal impairment is considered acceptable. In Scientific Advice (EMA/CHMP/SAWP/689338/2018), a PK study of sulindac in subjects with renal impairment was not deemed necessary since the PK properties of sulindac are well known and have been studied in renal impairment. The applicant presented the limited available data from studies of sulindac in subjects with severe renal impairment and ESRD. There are apparently no data on sulindac in subjects with moderate renal impairment. Sulindac is contraindicated in severe renal impairment. The applicant's proposal that patients with moderate renal impairment should not be treated with Flynpovi is endorsed.

- ***Impaired hepatic function***

The lack of a dedicated study of eflornithine in subjects with hepatic impairment is acceptable. In Scientific Advice (EMA/CHMP/SAWP/689338/2018), it was agreed that that a PK study of eflornithine in hepatic impairment was not warranted given that studies with eflornithine show that CYP/UGT and transporter based drug-drug interactions are unlikely and the results of the dedicated renal impairment study indicating that more than 70% of the absorbed dose of eflornithine was excreted unchanged into the urine.

The lack of a dedicated study of sulindac in subjects with hepatic impairment is acceptable. In Scientific Advice (EMA/CHMP/SAWP/689338/2018), it was agreed that further studies were not necessary for sulindac since its PK properties are well known and have been studied in subjects with hepatic impairment.

Flynpovi is contraindicated in severe hepatic impairment. Limited data are available for sulindac in mild/moderate hepatic impairment, which is appropriately reflected in the SmPC together with cautionary wording. It is agreed that patients with mild to moderate hepatic impairment can be treated at the regular Flynpovi dose with caution and regular monitoring.

- ***Gender***

It is agreed that no dose adjustment is necessary in terms of gender.

- ***Race***

It is considered unlikely that a dose adjustment would be needed in terms of race once body weight and organ function are accounted for.

- ***Weight***

The applicant presented the expected exposures of eflornithine and sulindac in FAP patients at the low and high extremes of weight. Eflornithine Cmax is approximately 2-fold higher, and sulindac Cmax and AUC are approximately 2.4-fold higher, in subjects with low compared to high body weight.

The applicant contends that, as the overall exposure of eflornithine in terms of AUC is the same regardless of weight, there are no anticipated impacts on safety and efficacy. For sulindac, the applicant does not anticipate an impact on safety as doses up to 2.6-fold higher than the Flynpovi dose have been investigated.

The applicant presented adverse event data from the PSCA study in one subject with weight below 50 kg and 4 subjects with weight ≥ 135 kg on the eflornithine-sulindac arm. All but one of the reported adverse events were considered unrelated or unlikely related to the study drugs and there was no change in dose for any adverse event. These data support the applicant's conclusion that differences in exposure in low and high body weight subjects are not expected to impact safety.

To evaluate if weight played a role in the efficacy of sulindac administered either as a single agent or in the combination, the applicant assessed efficacy endpoints of subjects weighing >135 kg in the CPP FAP-310 and the PSCA trials. Despite the limited number of patients in this evaluation (n=5), it is agreed that the results suggest that efficacy is not compromised in patients of high body weight.

- ***Elderly***

Despite the limited number of elderly patients included in the popPK analysis, it is agreed that once renal function is accounted for, the impact of age on eflornithine clearance is unlikely to be clinically relevant. It is also agreed that the dose of sulindac in Flynpovi is half the dose approved for rheumatoid arthiritis and, therefore, is considered appropriate for elderly people without renal/hepatic impairment. The SmPC reflects the limited data in elderly patients together with an appropriate cautionary wording.

Since no subjects ≥85 years have been treated with Flynpovi, the applicant has included a statement in the SmPC that there are no data in these subjects and therefore use of Flynpovi is not recommended.

***Interactions***

Study 749N-1603 assessed the inducing potential of eflornithine towards CYP1A2, 2B6 and 3A4, and also towards UGT1A1, 1A3, 1A9 and 2B7. The applicant concluded that no inducing potential from eflornithine has been identified towards these enzymes. Except CYP1A2, this conclusion cannot be supported. Considering the worst estimated concentrations at systemic and intestinal level (only for CYP3A4), 2,15mM and 0,98 mM, respectively, clinically relevant DDI due to eflornithine inducing effect towards CYP3A4 and CYP2B6 cannot be excluded. Therefore, the applicant committed to perform a mechanistic static model assessing eflornithine to assess the risk of inducing CYP3A4 and CYP2B6 as a post-authorisation commitment.

The applicant justified the lack of a study investigating eflornithine as a substrate of the uptake transporters OATP1B1 and OATP1B3. In study 749D-1604, the hepatic uptake of eflornithine by OATP1B1 and 1B3 was evaluated in cryopreserved human hepatocytes. Rosuvastatin and verapamil were utilised as positive and negative transport controls, respectively. Results showed that eflornithine does not have active hepatocyte uptake *in vitro* through these transporters.

According to eflornithine solubility profile, no DDIs are expected between eflornithine and proton-pump inhibitors or H2-receptor antagonists. In addition, no DDIs are expected between eflornithine and metal-containing antacids such as aluminium and magnesium.

During the evaluation, the applicant provided clinical data on the DDI between sulindac and probenecid, dimethyl sulfoxide, mifepristone, cardiac glycosides and zidovudine (data not shown). With probenecid, cardiac glycosides and zidovudine, no relevant and reliable clinical data allow a DDI with sulindac to be anticipated. Concurrent use of dimethyl sulfoxide and sulindac is not recommended since this has been shown to lead to both a reduction in plasma levels of the active sulphide metabolite and to causing peripheral neuropathy. NSAIDs should not be used for 8 - 12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

**Pharmacodynamics**

The pharmacodynamic properties of eflornithine and sulindac were not specifically investigated in the current application. However, the pivotal phase 3 study in subjects with FAP (CPP-FAP-310) included a urine polyamine analysis and a pharmacogenetic analysis.

***Primary pharmacology – urine polyamine analysis***

The purpose of the urine polyamine analysis in study CPP-FAP-310 was to evaluate the impact of treatment with eflornithine, sulindac or the combination of eflornithine and sulindac on the urinary polyamine content in patients with FAP.

Monoacetylspermidine (both $N^1$ and $N^8$ forms) are the major polyamine species found in human urine and are substrates for mammalian polyamine exporters. After 6 months of treatment, a statistically significant decrease in both $N^8$-acetylspermidine and $N^1$-acetylspermidine levels from baseline was observed in subjects treated with CPP-1X+Sulindac and subjects treated with CPP-1X alone, but not in subjects treated with Sulindac alone. There was no significant difference in the percent change from baseline between CPP-1X+Sulindac vs CPP-1X alone groups.

Decarboxylated S-adenosylmethionine accumulates in urine when the substrates putrescine and spermidine are suppressed by ODC inhibitors like eflornithine. After 6 months of treatment, a statistically significant increase in decarboxylated SAM levels from baseline was observed in subjects treated with CPP-1X+Sulindac and subjects treated with CPP-1X alone, but not in subjects treated with Sulindac alone. The percent change from baseline was significantly higher for CPP-1X+Sulindac vs CPP-1X alone groups.

Overall, the results suggest a similar effect of CPP-1X+Sulindac and CPP-1X alone treatments on urinary polyamine levels in patients with FAP.

***Secondary pharmacology***

Please see the Non-Clinical section.

***Pharmacodynamic interactions***

PD interactions with sulindac are well known and adequately detailed in the proposed SmPC.

The applicant has outlined the drugs which may interact pharmacodynamically with eflornithine. As the potential for hearing loss and haematopoietic changes are appropriately reflected in the SmPC.

***Genetic differences in PD response – pharmacogenetic analysis***

The pharmacogenetic analysis conducted in the phase 3 study (CPP-FAP-310) in patients with a genetic risk of colorectal cancer, found that delay in clinically relevant FAP-related events was associated with ODC+316 genotype, particularly in patients treated with eflornithine alone. In subjects treated with CPP-IX alone, those with the major allele (genotype GG) had a fewer events and time to event was delayed compared to the subjects with the minor allele (genotype GA or GA+AA) (p=0.01).

***Relationship between plasma concentration and effect***

A relationship between eflornithine/sulindac exposures and effect in patients with FAP has not been established.

## 2.4.5. Conclusions on clinical pharmacology

A limited number of clinical studies were presented to characterise the clinical pharmacology of eflornithine/sulindac FDC for the current application, with the applicant relying on data from the published

literature to complete the remainder of the clinical pharmacology package. This is not considered to be a major issue since both active substances are well known.

## *2.5. Clinical efficacy*

### 2.5.1. Dose response study

No dose response studies were performed.

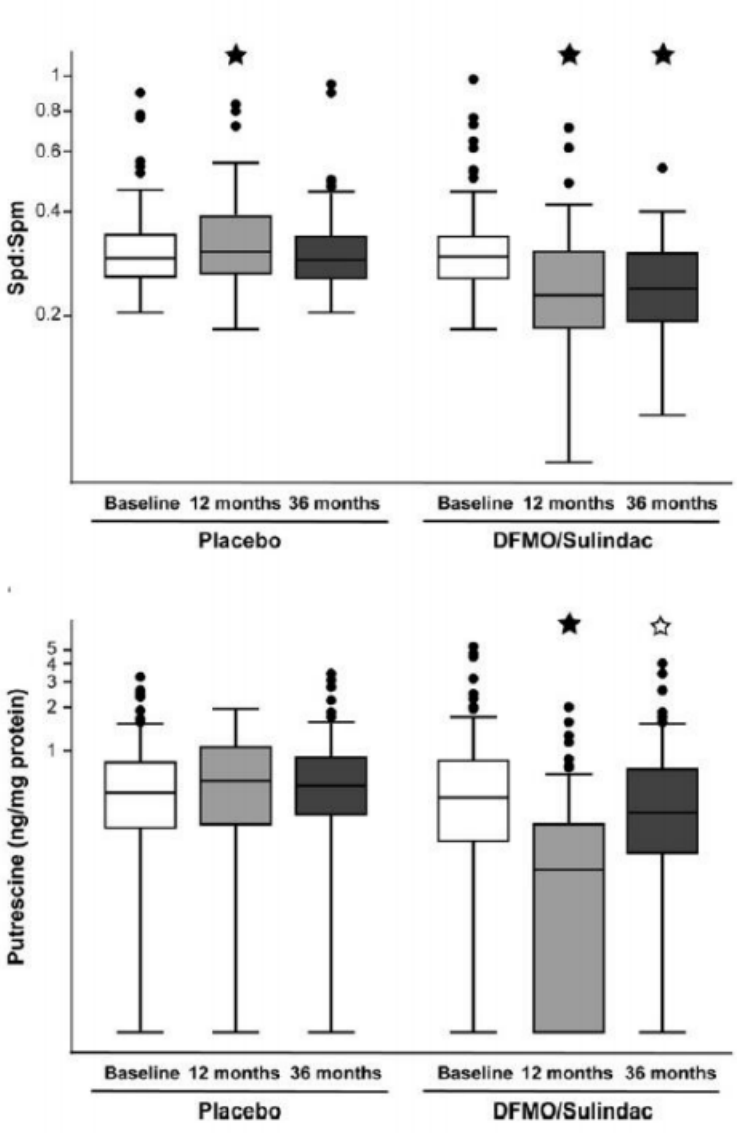
In the dossier the applicant has provided information solely based on publications to substantiate the choice of eflornithine 750 mg and sulindac 150 mg as proposed, as well as to support the biological rationale for this combination in treatment of FAP.

The rationale for selection of the eflornithine and sulindac doses included both preclinical and clinical evidence and considerations around efficacy and safety. Doses of eflornithine in humans of 0.2 g/m2 administered orally once daily (which corresponds to a dose of 500 mg per day for adults) achieved serum eflornithine concentrations which have been shown to inhibit ODC activity in cell culture (Creaven, et al., 1993; Meyskens, et al., 1998).

A dose de-escalation study was conducted to identify low doses that were effective in suppressing polyamine contents in the GI tract (Meyskens, et al., 1994). This dose de-escalation study was then followed by a 4-arm, placebo-controlled randomised study comparing 3 low eflornithine doses (75, 200 and 400 mg/m2 /day equating to 120 mg, 320 mg, and 640 mg based on a 1.6 m2 body surface area) in suppressing the polyamine content in the GI tract to determine an effective low dose for clinical studies (Meyskens, et al., 1998). Therefore, using 1.6 $m^2$ as the average surface area of a human adult (Reagan-Shaw, et al., 2008), a dose of 500 mg was chosen as the eflornithine dose for further human studies.

Subsequent Phase 2 studies showed that combining eflornithine (500 mg per day) with sulindac (150 mg per day) was safe and suppressed target tissue polyamine contents in a statistically significant manner (Thompson, et al., 2010).

In the combination treatment (E+S) group, spermidine-to-spermine ratio in rectal mucosa decreased between baseline and 12- and 36-month follow-up examinations (0.30, 0.23, and 0.24, respectively; $p<0.001$ for both comparisons to baseline. Putrescine levels decreased between baseline and 12 months (0.46 vs 0.15 nmol/mg protein; $p<0.001$) but rebounded between 12 and 36 months (0.15 vs 0.36 nmol/mg protein; $p=0.001$; Figure 8).




Abbreviations: DFMO=eflornithine; Spd: Spm= spermidine-to-spermine ratio
Source: Thompson, et al., 2010

**Figure 8: Polyamine levels at baseline, and after 12 and 36 months of treatment with eflornithine plus sulindac compared with placebo**

Clinical studies have documented anti-polyposis effects of sulindac administered orally in the 100 to 400 mg per day dose range in patients with FAP patients (Giardiello, et al., 2002). A randomised phase 2b demonstrated that a dose of 150 mg sulindac per day versus twice daily produced comparable results in regression and inhibition of sporadic adenomas. Therefore, sulindac at a dose of 150 mg was selected for Study CPP FAP-310 (DiSario, et al., 1997). A study was conducted to assess the effects of the APC gene mutation in FAP on ODC activity and polyamine levels comparing individuals with the germ-line mutation to genotype negative family members (Giardiello, et al., 1997). These results demonstrated ODC activity and polyamine levels are significantly elevated in gene carriers of FAP. As such, in the CPP FAP-310 study, the eflornithine dose was increased by 50% because of the 2.5-fold increase in baseline ODC in patients with germline APC mutations compared to patients without FAP (Giardiello, et al., 1997).

## 2.5.2. Main study

## CPP-FAP-310

**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)**

### *Methods*

### *Study Participants*

This study was conducted at 17 sites in the US, Canada, Belgium, Germany, the Netherlands, Spain, and the United Kingdom

Inclusion Criteria

Male and female subjects ≥18 years of age

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: hundreds to thousands of colorectal adenomatous polyps, usually appearing in teenage years

2. UGI endoscopy/lower gastrointestinal (LGI) endoscopy (proctoscopy/colonoscopy) performed within 30 days of randomisation.

3. Subjects with an intact colon/rectum and for whom prophylactic surgery was being considered as a stratification site.

4. Rectal/pouch polyposis as a stratification site, as follows:

    a. At least 3 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 (summarised as follows):

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

    Stage 2: 10 to 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.)

    b. For all subjects, any rectal/pouch polyps >5 mm must have been excised at baseline.

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

    a. Current Spigelman Stage 3 or 4. (Modified Spigelman Score and Classification).

    b. Prior surgical endoscopic intervention within the past 6 months for Spigelman Stage 3 or 4 that may have been down-staged to Spigelman Stage 1 or 2.

6. Haematopoietic status (within 30 days prior to randomisation):

    a. No significant haematologic abnormalities

    b. White blood cell count >/= 3,000/mm3

    c. Platelet count >/= 100,000/mm3

    d. Haemoglobin >/= 10.0 g/dL

    e. No history of clinical coagulopathy

7. Hepatic status (within 30 days prior to randomisation):

    a. Bilirubin no greater than 1.5 × the upper limit of normal (ULN)

    b. Aspartate aminotransferase and alanine aminotransferase no greater than 1.5 × ULN

    c. Alkaline phosphatase no greater than 1.5 × ULN

8. Renal status indicated creatinine no greater than 1.5 × ULN within 30 days prior to randomisation.

9. No clinically significant hearing loss, defined in Section 9.3.2, Exclusion Criterion 9.

10. If female, neither pregnant nor lactating.

11. If female of child-bearing potential, had a negative pregnancy test. Fertile subjects must use effective contraception. Confirmation of postmenopausal status unless surgically sterile.

12. Absence of gross blood in stool; only red blood on toilet paper was acceptable.

13. No discrete gastric or duodenal ulcer >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 weekly acceptable.

17. No concurrent warfarin, fluconazole, lithium, Pradaxa® or other direct thrombin inhibitors, Plavix®, cyclosporine, other NSAIDs (such as ibuprofen, aspirin in excess of 700 mg weekly, diflunisal), diuretics (furosemide and thiazides), dimethylsulfoxide, methotrexate, probenecid, propoxyphene hydrochloride, or Tylenol (acetaminophen) preparations containing aspirin or cytotoxic chemotherapy drugs.

18. Willingness to forego concurrent use of supplements containing omega-3 fatty acids, oral corticosteroids, NSAIDs, or other FAP-directed drug therapy.

19. Ability to provide written informed consent and follow protocol requirements.

<u>Exclusion Criteria</u>

Any of the following was regarded as a criterion for exclusion from the study:

1. Prior pelvic irradiation.

2. Receipt of oral corticosteroids within 30 days of enrolment.

3. Treatment with other investigational agents in the prior 4 weeks.

4. Use of other NSAIDs (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 enrolment.

7. Hypersensitivity to cyclooxygenase-2 inhibitors, sulfonamides, NSAIDs, or salicylates; NSAID-associated symptoms of gastritis.

8. Subjects must not have cardiovascular disease risk factors, as defined by:

- 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
- Known uncontrolled hyperlipidaemia, defined as low-density lipoprotein-C >/=190 mg/dL or triglycerides >/=500 mg/dL

9. Subjects with significant hearing loss (defined as hearing loss that affected everyday life and/or for which a hearing aid was required) were not eligible for study participation.

10. Intact colon/rectum or retained rectum or ileal pouch:

    a. Cancer on biopsy

    b. High-grade dysplasia found on polyp biopsy in which the polyp was not completely removed

    c. A large polyp (>1 cm) was not completely removed.

11. Duodenal cancer on biopsy.

12. Intra-abdominal desmoid disease Stage 3 or 4

13. Inability to provide informed consent.

## *Treatments*

Subjects received one of the following once-daily, oral, study drug regimens:

- CPP-1X 750 mg + sulindac 150 mg
- CPP-1X placebo + sulindac 150 mg
- CPP-1X 750 mg + sulindac placebo

for 24 months and, based on date of randomisation, 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 randomised subjects reached a minimum of 24, 36, 42, or 48 months of treatment:

Subjects took 4 tablets (3 CPP-1X [or matching placebo] and 1 sulindac [or matching placebo] as per randomisation) of study drug once daily with food at the same time of day, preferably in the morning.

## *Objectives*

<u>Primary Objective</u>

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 randomisation 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.

Secondary Objectives

*Protocol Version 2.1- 10 June 2013*

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 objectives included:

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.

*Protocol Version 5.2- 17 January 2019*

Secondary Efficacy objectives included:

Any improvement observed by the investigator during upper gastrointestinal (UGI) and lower gastrointestinal (LGI) visualisation (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.

## *Outcomes/endpoints*

### Primary Efficacy Endpoint: Time to First FAP-Related Event

The time from the date of randomisation to the date of the first occurrence of any FAP-related event at any disease site (colon/rectum/pouch, duodenum) led to discontinuation of study drug.

Follow-up of the subject for FAP-related events continued until 30 days after the last dose of study drug.

FAP-related events by disease site were as follows:

1. Preoperative, intact colon:
    a. 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 >/=10mm 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.

Baseline Endoscopy

Colonoscopy or flexible sigmoidoscopy was used to assess the colon, rectum, or neo-rectum (ileal pouch) and video images were captured for archiving and subsequent review. The last images were retroflexed pictures of the distal rectum or pouch at the anorectal ring. One pass was performed. Methods are described in Section 9.1 of the protocol; further details were provided in the Investigator and Site Training Manual.

Duodenal assessment used a forward and/or side-viewing endoscope with video images captured for subsequent review. The Spigelman classification at screening was utilised to stage the initial extent of disease and assess subject eligibility. A side-viewing scope may have been used to improve assessment of the ampulla of Vater/papilla. Ampullary biopsies (with histology) and snare excisions were performed per protocol, Investigator's Manual and institution's standard of care; results of these procedures were used as the subject's baseline Spigelman classification. The screening stage was the initial Spigelman stage (extent of polyposis combined with histology) and the baseline Spigelman stage was the post-snare intervention.

Follow-Up Endoscopies

Post-baseline endoscopies were performed every 6 months. At any assessment, if any subject required an excisional intervention or had duodenal Spigelman stage progression (Stage 2, 3, or 4), the subject was considered to have an FAP-related event and study drug was discontinued

Imaging Submission

All images were captured on DVD or flash drive, de-identified, and forwarded to a central imaging laboratory for archiving. All data were de-identified in regard to subject, site, and treatment, but subject study identification number was available for baseline and subsequent comparison, as appropriate. This process was defined in detail and included in the Image Preparation and Submission Guidelines for still and video endoscopy image submission. No independent review of endoscopy images was performed.

## Secondary Efficacy Outcome and Analysis

Any improvement observed by the investigator during upper gastrointestinal (UGI) and lower gastrointestinal (LGI) visualisation (i.e. endoscopy and colonoscopy) at the 6 and 12-month study visits was to be described using the variables UGI Observed Improvement (UGIOI), and LGI Observed Improvement (LGIOI). Each patient had to have one pair of UGIOI and LGIOI outcomes.

Protocol 5.2 (17 January 2019):

4.5. Secondary Outcomes

Secondary Efficacy Analyses: Any improvement observed by the investigator during upper gastrointestinal (UGI) and lower gastrointestinal (LGI) visualisation (i.e. endoscopy and colonoscopy) at the 6 and 12-month study visits was toill 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).

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 analysed 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.

## *Sample size*

The following reflects the possible range of FAP-related events that could have been observed.

**Table 11: Overall event-free proportions after 2 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 |

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

Sample size calculation

Assuming a two-sided alpha of 0.05, an overall two-year event free proportion of 60% in the combination treatment arm and 30% in each single treatment arm and a randomisation ratio of 1:1:1, a sample size of 50 per group was estimated to yield at least 85% power to detect a treatment effect comparing either of the two single treatment arms to the combination arm using a 2-sided stratified log-rank test.

Assuming exponentially distributed time-to-event, the assumed minimum clinically important hazard ratio is 0.4243 for comparison of the combination arm to each single treatment arm, corresponding to a median time to event of 32.6 months in the combination arm and 13.8 months in each of the single treatment arms. 55 events for each two-arm comparison are expected within 24 months under these assumptions.

A blinded sample size reassessment based on pooled data was also planned (see Statistical Methods).

## *Randomisation*

Eligible subjects were randomised 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).

A centralised randomisation process was used to balance treatment groups within disease prognostic strata. The event prognosis groups were 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 had 2 or more of these disease sites, the most severe prognosis stratum was assigned for randomisation (e.g., worst > intermediate > best). Since a subject may have had more than 1 disease site involved, the study assessed time to any defined FAP-related event in the subject as a whole.

## *Blinding (masking)*

The study drug was provided in a double-blind manner. Neither the subject, investigator, clinic staff, nor CPP knew which combination was being administered.

## *Statistical methods*

*Statistical Analysis Plan*

Details of the statistical methods provided in this section are as described in version 5.2 of the Statistical Analysis Plan, dated 25 January 2019 and version 5.2 of the protocol, dated 17 January 2019.

**Table 12: Summary of SAP amendments**

| SAP Version # | Date | Description of SAP Amendment |
|---|---|---|
| Ver 1.3 | 1-Aug-12 | First Version of the SAP to the IND |
| Ver. 2.0 | 11-Apr-13 | Administrative changes; Updated Study overview for consistency with protocol; Revisions to study objections and Primary hypothesis testing; Added Section 3.2.2 Secondary Efficacy Analysis; Section 5.1 Determination of Sample and Statistical Methods - section was rewritten. Section 5.2 Data Monitoring Committee - section was rewritten; Added Section 5.4 Health Related Quality of Life analysis |
| Ver. 3.0 | 30-Sep-14 | Administrative changes, clarifications to section 5.2, Data Monitoring Committee, as it relates to the planned futility analysis. Added additional text to futility analysis as follows: "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." |
| Ver. 4.0 | 15-Feb-16 | Administrative changes, added clarification to Section 4.4 Other Populations, specifically the Per Protocol Population; added clarifications to the futility analysis and assessment. Section 5.2 Interim Futility Analysis Details added the following: When 45 adjudicated primary endpoints have occurred, corresponding to when 50% of maximum trial information has been amassed."<br>Second column – Description: Updated to read as follows:<br>Efficacy criterion Z=1.96 at terminal analysis.<br>Futility criterion of Z=0.50 or less at interim analysis.<br>Total Type I error for end of study comparison = 0.0471.<br>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. Added new Section 5.2.2 on the Adjudication Committee (AC). Section 5.3.2 Patient disposition and Treatment summaries, added clarifications. Removed the TLFs as an Appendix SAP and will be a stand alone document. |
| Ver 4.1 | 27-Dec-16 | Administrative clarifications to Section 5.2.1 Data Monitoring and Clinical Events Committee (CEC) - title revised from adjudication committee, revised section to provided more details on how the committee will function. Provided clarifications to Section 5.3.6 General Procedures for Handling of Missing Data. |
| Ver. 4.2 | 15-May-17 | Administrative clarifications. Section 5.2.1, Revisions to the Futility Analysis description with additional details, and tables for the planned analysis. |
| Ver. 4.3 | 20-Jul-17 | Administrative clarifications, Section 5.2.2 Clinical Events Committee. |
| Ver. 5.0 | 2-Apr-18 | Administrative clarifications; Revision of Section 5.1, deletion Section 5.2.2 Clinical Events Committee. |
| Ver. 5.1 | 30-Jul-18 | Section 3.2.2 Revision to what and how secondary endpoints will be analyzed. |
| Ver. 5.2 | 25-Jan-19 | Added clarifications to Section 3.2.1 (new sub-section) for the Primary Analysis |

*Changes in the planned analyses presented in the CSR*

The SAP discussed 11 disease site subgroups to explore the subcategories of FAP-related events. In the final analysis, instead of performing exploratory (post hoc) analysis in each of the 11 disease site subgroups, combinations of those disease site subgroups and combinations of subcategories of FAP-related events were formed to explore and characterise the observed nominal benefit of combination therapy in ways perceived to be clinically meaningful. Post-hoc analyses were also performed that censored 2 events not considered clinically meaningful by either the FDA (excision of ≥10 mm rectal or pouch polyp) or EMA (Spigelman stage progression).

*Analysis Populations*

- The **intent-to-treat population** includes all patients that have been randomised to one of the three study arms. Patients will be analysed in the group to which they were randomised, whether or not they received their assigned treatment, any treatment whatsoever, or completed their treatment course and follow-up.
- 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 analysed in the treatment group according to which actual treatment was initially received.

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

*Analysis of primary efficacy endpoint*

The primary analysis was to be a time-to-event analysis using the stratified log-rank test. The stratified Cox proportional hazards regression models was to be used for secondary assessments. Graphical analyses (log-minus-log plots) were to be used to check the assumption of constant hazard ratios. The strata are the patient's site of disease involvement at baseline: rectal/pouch polyposis, duodenal polyposis, and pre-colectomy.

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

Patient follow-up will be analysed in continuous time, although it is recognised 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.

Censoring rules:

- 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.
- 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 randomisation.

Every effort was to be made to minimise the occurrence of censoring and missing data.

Sensitivity analysis

Prior to the primary analysis, balance was to be assessed between the three arms in terms of key potential confounders measured at the baseline visit. If significant imbalance in any of these variables was found using a 2 degree of freedom test of homogeneity at the 0.01 level of significance, it was to be incorporated into a sensitivity 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) was to serve only as a secondary analysis to aid in the interpretation of the primary result.

Post-hoc analyses

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.

*Analysis of secondary efficacy endpoints – Upper/Lower Gastrointestinal Observed Improvement*

The null hypothesis of no association between treatment group and Improvement endpoints was tested using the exact Mantel-Haenszel procedure across the 3 randomisation strata. For each of the 2 treatment comparisons, exact Mantel-Haenszel p-values were calculated for both the UGI and LGI assessments (using the point-probability method based on the convolution of 3 independent central hypergeometric distributions).

*Type I error control*

The SAP states that the overall type I error for the primary endpoint across the two treatment comparisons was to be controlled using a hierarchical testing procedure as follows:

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

The SAP plan states that overall type I error for the secondary efficacy analysis was to be 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. The testing procedure controlled the type I error across the two treatment comparisons for each secondary endpoint separately. It did not control the type I error across both secondary endpoints.

*Subgroup analyses*

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

*Multicentre study*

No adjustments for centre or region were planned in statistical analyses of the primary endpoints.

*Interim analyses*

One interim analysis for sample size reassessment and one interim efficacy and futility analysis were planned.

<u>Interim analysis for sample size reassessment</u>

The DMC was to assess the observed trial event rate based on pooled data only using data from a single time point, when enrolment was approximately 95% complete. They were to 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 was, if possible, to estimate the overall observed event rate and 90% confidence interval. If this type of assessment was not possible, then an assessment was to be performed taking into consideration the total number of subjects randomised, total number of events, total number of dropouts, and cumulative study safety data.

<u>Interim efficacy and futility analysis</u>

A pre-specified, blinded, interim efficacy and futility analysis was planned to be performed after a total of 45 primary endpoints had occurred, which represented 50% of expected maximum trial information, or as soon thereafter as possible. The analysis was to be performed for each of the two treatment comparisons contained in the primary objective. Note that the combination arm was specified as the reference treatment group in the description below.

The efficacy analysis was to use a modified Haybittle-Peto stopping rule based on the stratified logrank Z-score. If that Z-score equalled or exceeded 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.

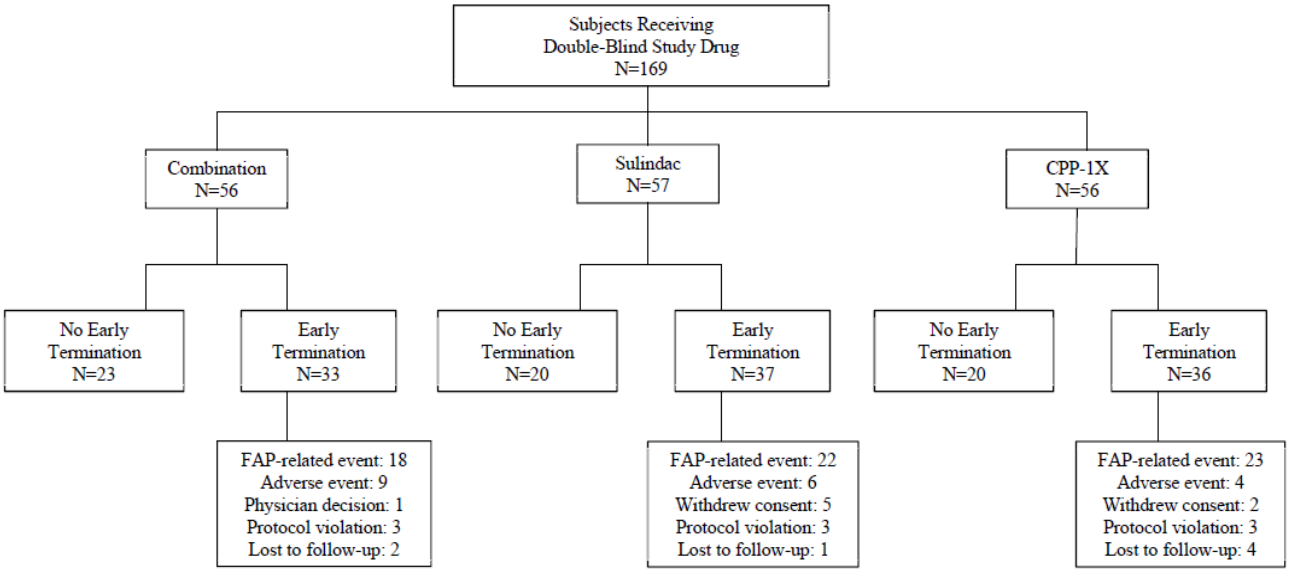
Assuming this is not the case and the trial continued to its planned end, the Z-score criterion for declaring significance at the 5% level at the end of the trial was to be increased in magnitude to plus or minus 1.962 in order to preserve the overall type I error rate for the trial at 0.05.

The futility analysis was to use a one-sided futility stopping criterion of Z=-0.50. That is, if the stratified log-rank Z-score was less than or equal to -0.50, an investigation was to 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%.

## *Results*

## Participant flow

Per protocol, in the absence of a FAP-related event, subjects received study drug for 24 to 48 months. The final decision concerning the study end date, if prior to 30 April 2019, was to be 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.




FAP=familial adenomatous polyposis
Source: Table 14.1.1.1

**Figure 9: Disposition of subjects**

**Table 13: Summary of subject disposition (all enrolled subjects)**

| | Combination | Sulindac | CPP-1X |
|---|---|---|---|
| ITT Population, n | 56 | 58 | 57 |
| Safety Population, n | 56 | 57 | 56 |
| Randomized but not treated, n (%) | 0 | 1 (1.7) | 1 (1.8) |
| Completed treatment period (months), n (%) | | | |
| >0-12 | 14 (25.0) | 19 (32.8) | 15 (26.3) |
| >12-24 | 12 (21.4) | 13 (22.4) | 19 (33.3) |
| >24-36 | 16 (28.6) | 14 (24.1) | 14 (24.6) |
| >36-48 | 12 (21.4) | 11 (19.0) | 5 (8.8) |
| >48 | 1 (1.8) | 0 | 1 (1.8) |
| Median | 24.3 | 18.5 | 21.9 |
| Interquartile range | 24.0 | 20.8 | 19.2 |
| Completed study without event, n (%) | 23 (41.1) | 21 (36.2) | 21 (36.8) |
| Completed study due to FAP-related event, n (%) | 18 (32.1) | 22 (37.9) | 23 (40.4) |
| Did not complete the study, n (%) | 15 (26.8) | 15 (25.9) | 13 (22.8) |
| Reason for early termination, n (%) | | | |
| Adverse event | 9 (16.1) | 6 (10.3) | 4 (7.0) |
| Withdrew consent | 0 | 5 (8.6) | 2 (3.5) |
| Physician decision | 1 (1.8) | 0 | 0 |
| Protocol violation | 3 (5.4) | 3 (5.2) | 3 (5.3) |
| Lost to follow-up | 2 (3.6) | 1 (1.7) | 4 (7.0) |
| Completed 30 days off treatment follow-up, n (%) | | | |
| Yes | 52 (92.9) | 51 (87.9) | 49 (86.0) |
| No | 4 (7.1) | 7 (12.1) | 8 (14.0) |

FAP=familial adenomatous polyposis; ITT=Intent-to-Treat
Note: Percentages are based on total number of subjects in the ITT Population in each column.
Source: Table 14.1.1.1

## Recruitment

First patient enrolled: 2 December 2013

Last patient completed: 12 November 2018

Database lock: 8 March 2019

This study was conducted at 17 sites in the US, Canada, Belgium, Germany, the Netherlands, Spain, and the United Kingdom.

## Conduct of the study

Protocol amendments

Protocol version 1.2 (27 February 2012) was the first formal protocol submitted to the FDA. Since that version, the protocol was amended 11 times. Three of these amendments were substantial (Protocol

versions 3.0, 4.0, and 5.0). Protocol version 2.0 was the protocol used for study initiation in the US and Canada and version 2.1 was used for study initiation in the EU.

Protocol Deviations

A total of 24 subjects had protocol deviations that resulted in their exclusion from the Per Protocol Population.

**Table 14: Summary of Protocol deviations resulting in exclusion from the per protocol population (ITT population)**

| | Combination N=56 | Sulindac N=58 | CPP-1X N=57 |
|---|---|---|---|
| **Classification** | **n (%) of Subjects** | | |
| Subjects with protocol deviation | 9 (16.1) | 10 (17.2) | 5 (8.8) |
| Protocol deviation classifications | | | |
| Entrance criteria[a] | 0 | 1 (1.7) | 0 |
| Dosing[b] | 2 (3.6) | 3 (5.2) | 3 (5.3) |
| Study procedures[c] | 0 | 0 | 1 (1.8) |
| Randomized but not treated[d] | 0 | 1 (1.7) | 1 (1.8) |
| No postbaseline endoscopy assessment[e] | 6 (10.7) | 6 (10.3) | 2 (3.5) |
| Other[f] | 1 (1.8) | 0 | 0 |

APC= adenomatous polyposis coli; ITT=Intent-to-Treat

[a] Evidence of APC testing not found (Subject 103150).

[b] Subject missed >90 days of study drug dosing: Subjects 117167 and 122194 (CPP-1X + sulindac), 113029, 113244, and 117140 (placebo + sulindac), 101192, 117111, and 121235 (CPP-1X + placebo).

[c] Biopsy not taken during upper gastrointestinal endoscopy (Subject 117111).

[d] Subjects 110080 (placebo + sulindac) and 119126 (CPP-1X + placebo).

[e] Subjects 101051, 102216, 108124, 110119, 118146, and 119232 (CPP-1X + sulindac), 101250, 110080, 111086, 113016, 113189, and 119093 (placebo + sulindac), 111170 and 119126 (CPP-1X + placebo).

[f] Subject missed >90 days of study drug dosing (Subject 104217).

## Baseline data

**Table 15: Summary of demographics and baseline characteristics (ITT population)**

| Characteristic | Combination N=56 | Sulindac N=58 | CPP-1X N=57 | Overall N=171 |
|---|---|---|---|---|
| Age (years) | | | | |
| Mean (SD) | 37.8 (13.35) | 38.1 (13.66) | 39.7 (14.76) | 38.5 (13.88) |
| Median | 36.0 | 38.0 | 39.0 | 39.0 |
| Min, max | 18, 65 | 18, 71 | 18, 71 | 18, 71 |
| Age by FAP stratification (years) | | | | |
| Pre-colectomy | n=12 | n=13 | n=12 | n=37 |
| Mean (SD) | 27.4 (9.72) | 22.5 (3.71) | 23.2 (8.66) | 24.3 (7.82) |
| Median | 24.0 | 22.0 | 20.0 | 22.0 |
| Min, max | 18, 52 | 18, 30 | 18, 49 | 18, 52 |
| Duodenal polyposis | n=33 | n=34 | n=33 | n=100 |
| Mean (SD) | 41.5 (13.32) | 44.9 (11.41) | 44.7 (12.49) | 43.7 (12.40) |
| Median | 44.0 | 43.0 | 43.0 | 43.0 |
| Min, max | 18, 65 | 22, 71 | 22, 71 | 18, 71 |
| Rectal/pouch polyposis | n=11 | n=11 | n=12 | n=34 |
| Mean (SD) | 38.2 (11.59) | 35.3 (11.65) | 42.4 (14.05) | 38.7 (12.52) |
| Median | 35.0 | 36.0 | 41.5 | 39.5 |
| Min, max | 18, 54 | 21, 54 | 18, 65 | 18, 65 |
| Gender, n (%) | | | | |
| Male | 34 (60.7) | 37 (63.8) | 28 (49.1) | 99 (57.9) |
| Female | 22 (39.3) | 21 (36.2) | 29 (50.9) | 72 (42.1) |
| Reproductive status, n (%) | | | | |
| Childbearing potential | 14 (25.0) | 10 (17.2) | 17 (29.8) | 41 (24.0) |
| Postmenopausal | 2 (3.6) | 4 (6.9) | 4 (7.0) | 10 (5.8) |
| Surgically sterile | 6 (10.7) | 7 (12.1) | 8 (14.0) | 21 (12.3) |
| Ethnicity, n (%) | | | | |
| Hispanic or Latino | 5 (8.9) | 3 (5.2) | 5 (8.8) | 13 (7.6) |
| Not Hispanic or Latino | 50 (89.3) | 54 (93.1) | 50 (87.7) | 154 (90.1) |
| Not reported | 1 (1.8) | 1 (1.7) | 0 | 2 (1.2) |
| Unknown | 0 | 0 | 2 (3.5) | 2 (1.2) |
| Race, n (%) | | | | |
| Asian | 0 | 1 (1.7) | 0 | 1 (0.6) |
| Black or African American | 6 (10.7) | 3 (5.2) | 1 (1.8) | 10 (5.8) |
| White | 48 (85.7) | 50 (86.2) | 54 (94.7) | 152 (88.9) |
| Other | 2 (3.6) | 2 (3.4) | 2 (3.5) | 6 (3.5) |
| Multiple | 0 | 2 (3.4) | 0 | 2 (1.2) |
| Smoking history, n (%) | | | | |
| Never | 32 (57.1) | 44 (75.9) | 36 (63.2) | 112 (65.5) |
| Former | 14 (25.0) | 8 (13.8) | 10 (17.5) | 32 (18.7) |
| Current | 10 (17.9) | 6 (10.3) | 11 (19.3) | 27 (15.8) |
| Weight (kg) | n=55 | n=56 | n=57 | n=168 |
| Mean (SD) | 80.4 (17.04) | 80.3 (16.19) | 81.1 (21.12) | 80.6 (18.16) |
| Median | 78.5 | 79.2 | 83.5 | 79.7 |
| Min, max | 43, 136 | 50, 127 | 43, 122 | 43, 136 |
| Body mass index (kg/m$^2$) | n=53 | n=56 | n=57 | n=166 |
| Mean (SD) | 27.2 (5.89) | 27.2 (5.38) | 28.4 (7.72) | 27.6 (6.42) |
| Median | 26.0 | 26.3 | 26.7 | 26.3 |
| Min, max | 17, 50 | 18, 43 | 18, 63 | 17, 63 |

FAP=familial adenomatous polyposis; ITT=Intent-to-Treat; max=maximum; min=minimum; SD=standard deviation
Source: Table 14.1.4.1

Demographic and baseline characteristics were similar for the Safety Population (Table 14.1.4.2) and Per Protocol Population (Table 14.1.4.3).

Demographic data by subject are provided in Listing 16.2.4.1.

**Table 16: Summary of baseline disease characteristics (ITT population)**

| Characteristic | Combination N=56 | Sulindac N=58 | CPP-1X N=57 | Overall N=171 |
|---|---|---|---|---|
| FAP stratification, n (%) | | | | |
| Pre-colectomy | 12 (21.4) | 13 (22.4) | 12 (21.1) | 37 (21.6) |
| Duodenal polyposis | 33 (58.9) | 34 (58.6) | 33 (57.9) | 100 (58.5) |
| Rectal/pouch polyposis | 11 (19.6) | 11 (19.0) | 12 (21.1) | 34 (19.9) |
| FAP surgical status, n (%) | | | | |
| Pre-colectomy | 13 (23.2) | 13 (22.4) | 12 (21.1) | 38 (22.2) |
| Colectomy with IRA | 13 (23.2) | 19 (32.8) | 21 (36.8) | 53 (31.0) |
| Proctocolectomy with IPAA | 28 (50.0) | 21 (36.2) | 18 (31.6) | 67 (39.2) |
| Colectomy with ileostomy | 2 (3.6) | 5 (8.6) | 6 (10.5) | 13 (7.6) |
| FAP years since diagnosis[a] | | | | |
| Mean (SD) | 17.4 (10.43) | 15.5 (11.43) | 19.7 (11.50) | 17.5 (11.20) |
| Median | 16.0 | 12.5 | 19.0 | 16.0 |
| Min, max | 1, 40 | 0, 47 | 0, 43 | 0, 47 |
| Desmoids staging, n (%) | | | | |
| Stage 1 | 6 (10.7) | 5 (8.6) | 1 (1.8) | 12 (7.0) |
| Stage 2 | 0 | 2 (3.4) | 1 (1.8) | 3 (1.8) |
| Missing | 50 (89.3) | 51 (87.9) | 55 (96.5) | 156 (91.2) |

FAP=familial adenomatous polyposis; IPAA=ileal pouch anal anastomosis; IRA=ileorectal anastomosis; ITT=Intent-to-Treat; max=maximum; min=minimum; SD=standard deviation
[a] Years since diagnosis was calculated as (consent date - diagnosis date)/365.25.

**Table 17: Summary of compliance (ITT population)**

| | Combination N=56 | | Sulindac N=58 | CPP-1X N=57 |
|---|---|---|---|---|
| Missed dose, n (%) | | | | |
| Yes | 43 (76.8) | | 51 (87.9) | 47 (82.5) |
| No | 13 (23.2) | | 6 (10.3) | 9 (15.8) |
| Number of missed days | N=56 | | N=57 | N=56 |
| Mean (SD) | 40.2 (46.37) | | 42.0 (48.88) | 41.4 (43.96) |
| Median | 25.0 | | 26.0 | 28.0 |
| Min, max | 0, 230 | | 0, 220 | 0, 172 |
| Overall compliance | CPP-1X | Sulindac | | |
| | N=56 | N=56 | N=58 | N=56 |
| Mean (SD) | 75.9 (17.73) | 74.9 (17.70) | 71.8 (19.02) | 73.9 (14.10) |
| Median | 80.3 | 80.2 | 75.9 | 78.0 |
| Min, max | 13, 100 | 13, 100 | 0, 100 | 44, 100 |
| <80% | 28 (50.0) | 28 (50.0) | 38 (65.5) | 30 (52.6) |
| 80 – 120% | 28 (50.0) | 28 (50.0) | 20 (34.5) | 26 (45.6) |
| >120% | 0 | 0 | 0 | 0 |

ITT=Intent-to-Treat; SD = standard deviation

## Numbers analysed

The numbers of subjects in each study population are shown in Table 18.

**Table 18: Summary of data sets analysed**

| Population | Combination | Sulindac | CPP-1X |
|---|---|---|---|
| ITT Population[a], n | 56 | 58 | 57 |
| Safety Population[b], n (%) | 56 (100) | 57 (98.3) | 56 (98.2) |
| Per Protocol Population[c], n (%) | 47 (83.9) | 48 (82.8) | 52 (91.2) |

ITT=Intent-to-Treat

[a] Included all subjects who were randomized to 1 of the 3 treatment groups.

[b] Included all ITT subjects who received at least 1 dose of study drug.

[c] Included the subset of the ITT Population that fulfilled all protocol eligibility, intervention, and outcome assessments.

## Outcomes and estimation

### Primary Efficacy Endpoint: Time to First FAP-Related Event

A total of 63 subjects experienced an FAP-related event in this study. Time to first occurrence of any FAP-related event was a composite endpoint. In some incidences, the first occurrence of any FAP-related event included 2 concurrent events. Overall, the first FAP-related event with the highest frequency was progression in Spigelman stage. No disease progression events requiring life-altering surgery in the colon, retained rectum, or ileal pouch (i.e., LGI anatomy) were observed in the combination treatment group.

**Table 19: Composition of event that formed the primary efficacy endpoint by treatment group for all subjects (ITT population)**

| Event ID Event Description | Combination N=56 | Sulindac N=58 | CPP-1X N=57 | Overall N=171 |
|---|---|---|---|---|
| | n (%) of Subjects | | | |
| Subjects event-free | 38 (67.9) | 36 (62.1) | 34 (59.6) | 108 (63.2) |
| Subjects with ≥1 FAP-related event | 18 (32.1) | 22 (37.9) | 23 (40.4) | 63 (36.8) |
| 1. DP: need for colectomy | 0 | 4 (6.9) | 2 (3.5) | 6 (3.5) |
| 1. DP: need for colectomy,<br>6. Spigelman stage progression | 0 | 0 | 1 (1.8) | 1 (0.6) |
| 2. Surgical intervention to remove ≥10 mm polyp or HGD (snare, trans-anal) | 2 (3.6) | 2 (3.4) | 2 (3.5) | 6 (3.5) |
| 2. Surgical intervention to remove ≥10 mm polyp or HGD (snare, trans-anal)<br>3. DP: need for proctectomy | 0 | 1 (1.7) | 0 | 1 (0.6) |
| 2. Surgical intervention to remove ≥10 mm polyp or HGD (snare, trans-anal)<br>7. DP: need for duodenal excisional intervention | 0 | 1 (1.7) | 0 | 1 (0.6) |
| 3. DP: need for proctectomy | 0 | 0 | 1 (1.8) | 1 (0.6) |
| 4. DP: need for pouch resection | 0 | 1 (1.7) | 4 (7.0) | 5 (2.9) |
| 5. Cancer (rectum or pouch) | 0 | 0 | 0 | 0 |
| 6. Spigelman progression | 10 (17.9) | 4 (6.9) | 10 (17.5) | 24 (14.0) |
| 6. Spigelman progression,<br>7. DP: need for duodenal excisional intervention | 1 (1.8) | 3 (5.2) | 1 (1.8) | 5 (2.9) |
| 7. DP: need for duodenal excisional intervention | 5 (8.9) | 6 (10.3) | 2 (3.5) | 13 (7.6) |
| 8. Cancer (duodenum) | 0 | 0 | 0 | 0 |
| 9. Death | 0 | 0 | 0 | 0 |

DP=disease progression; FAP=familial adenomatous polyposis; HGD=high-grade dysplasia; ID=identification; IRA=ileorectal anastomosis; ITT=Intent-to-Treat

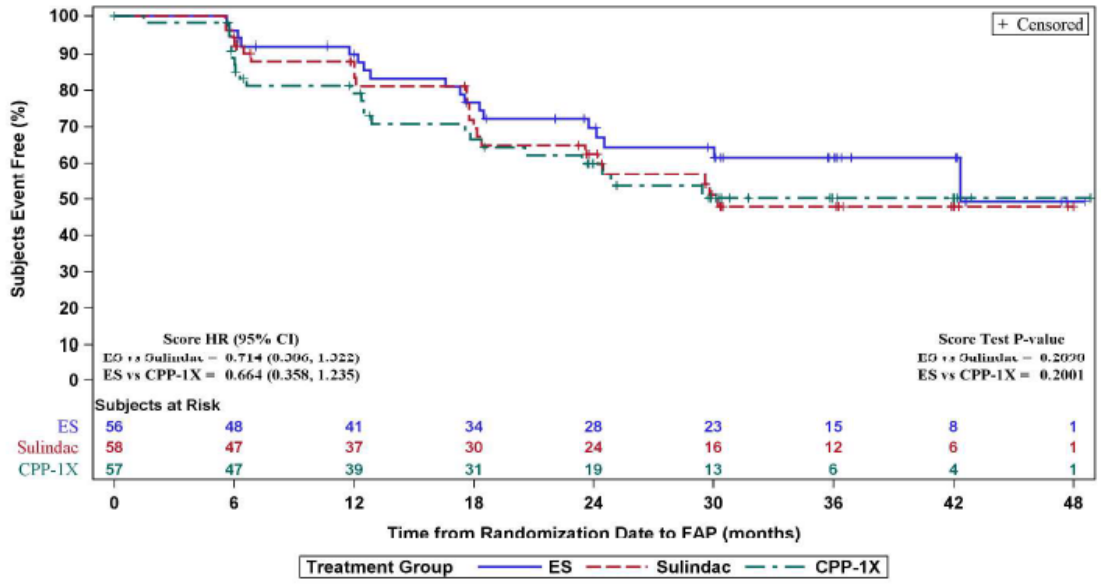
Note: Table includes only the first occurrence of any FAP-related events that were used for the primary efficacy endpoint. When a subject had 2 events on the same date, the 2 events are displayed together.

**Table 20: Distribution of all FAP-related events and surgeries by treatment group for all subjects (ITT population)**

| Event ID Event Description | Combination N=56 | Sulindac N=58 | CPP-1X N=57 | Overall N=171 |
|---|---|---|---|---|
| | n (%) of Subjects | | | |
| 1. DP: need for colectomy | 0 | 4 (6.9) | 3 (5.3) | 7 (4.1) |
| S: colectomy with IRA, total proctocolectomy | 0 | 2 | 0 | 2 |
| 2. Surgical intervention to remove ≥10 mm polyp or HGD (snare, trans-anal) | 2 (3.6) | 4 (6.9) | 2 (3.5) | 8 (4.7) |
| S: removed ≥10 mm polyp | 2 | 4 | 2 | 8 |
| S: HGD (snare, trans-anal) performed | 0 | 0 | 0 | 0 |
| 3. DP: need for proctectomy | 0 | 1 (1.7) | 1 (1.8) | 2 (1.2) |
| S: proctectomy | 0 | 1 | 0 | 1 |
| 4. DP: need for pouch resection | 0 | 1 (1.7) | 4 (7.0) | 5 (2.9) |
| S: pouch resection | 0 | 0 | 1 | 1 |
| 5. Cancer (rectum or pouch) | 0 | 0 | 0 | 0 |
| 6. Spigelman stage progression | 11 (19.6) | 7 (12.1) | 12 (21.1) | 30 (17.5) |
| Stage 3-4 | 5 | 5 | 8 | 18 |
| Stage <4 | 6 | 2 | 4 | 12 |
| 7. DP: need for duodenal excisional intervention | 6 (10.7) | 10 (17.2) | 3 (5.3) | 19 (11.1) |
| S: Submucosal resection | 2 | 5 | 2 | 9 |
| S: Trans-duodenal | 1 | 0 | 0 | 1 |
| S: Duodenectomy | 0 | 0 | 0 | 0 |
| S: Ampullectomy | 2 | 1 | 0 | 3 |
| S: Whipple procedure | 0 | 0 | 1 | 1 |
| 8. Cancer (duodenum) | 0 | 0 | 0 | 0 |
| 9. Death | 0 | 0 | 0 | 0 |
| 10. Number of subjects with any FAP-related event excluding Spigelman stage progression | 7 | 15 | 11 | 33 |
| 11. Number of subjects with any FAP-related event | 18 | 22 | 23 | 63 |

DP=disease progression; FAP=familial adenomatous polyposis; HGD=high-grade dysplasia; ID=identification; IRA=ileorectal anastomosis; ITT=Intent-to-Treat; S=surgery
Note: Table includes all FAP-related events and subsequent surgeries. A subject could have had more than 1 event.

Pre-specified Primary Analyses




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

**Figure 10: Time from randomisation to first occurrence of any FAP-related event (ITT population)**

**Table 21: Analysis of time from randomisation to first occurrence of any FAP-related event (ITT population)**

| | Combination N=56 | Sulindac N=58 | CPP-1X N=57 |
|---|---|---|---|
| Subjects with any FAP-related event, n (%) | 18 (32.1) | 22 (37.9) | 23 (40.4) |
| Subject-years of follow up | 11.06 | 11.49 | 13.45 |
| FAP-related event per subject year | 14 | 12 | 8 |
| Subjects censored, n (%) | 38 (67.9) | 36 (62.1) | 34 (59.6) |
| Hazard ratio[a] (95% CI) | | 0.71 (0.4, 1.3) | 0.66 (0.4, 1.2) |
| p-value vs. combination[b] | | 0.2898 | 0.2001 |

CI=confidence interval; FAP=familial adenomatous polyposis; ITT=Intent-to-Treat

Note: Time to event is defined as (date of event or censored date – randomization date + 1). Month is defined as 30.4375 days.

[a] Hazard ratio of probability of having an event was derived from the Cox proportional hazards model stratified by randomization strata.

[b] The hazard ratio 95% CI for each treatment group and the p-value for the between groups comparisons were derived from the stratified Cox proportional hazards model using the score method; an external SAS macro hazard ratio developed based on Lin DY et al.[61] was used to implement this analysis method.

No statistically significant difference between the combination treatment group and either single-agent treatment group for time from the date of randomisation to the date of the first occurrence of any FAP-related event was observed in the prespecified analyses by disease stratum group (pre-colectomy, duodenal polyposis, and rectal/pouch polyposis). (Table 22).

**Table 22: Analysis of time from randomisation to first occurrence of any FAP-related event by stratification (ITT population)**

| | Combination N=56 | Sulindac N=58 | CPP-1X N=57 |
|---|---|---|---|
| **Pre-colectomy stratum** | n=12 | n=13 | n=12 |
| Subjects with any FAP-related event, n (%) | 2 (16.7) | 6 (46.2) | 5 (41.7) |
| Subject-years of follow up | 1.62 | 3.70 | 3.12 |
| FAP-related event per subject year | 3 | 5 | 4 |
| Subjects censored, n (%) | 10 (83.3) | 7 (53.8) | 7 (58.3) |
| Hazard ratio[a] (95% CI) | | 0.30 (0.1, 1.3) | 0.20 (0.0, 1.3) |
| p-value[b] | | 0.1210 | 0.1076 |
| **Duodenal polyposis stratum** | n=33 | n=34 | n=33 |
| Subjects with any FAP-related event, n (%) | 12 (36.4) | 14 (41.2) | 13 (39.4) |
| Subject-years of follow up | 6.25 | 6.08 | 7.50 |
| FAP-related event per subject year | 19 | 16 | 11 |
| Subjects censored, n (%) | 21 (63.6) | 20 (58.8) | 20 (60.6) |
| Hazard ratio[a] (95% CI) | | 0.72 (0.3, 1.5) | 0.76 (0.3, 1.6) |
| p-value[b] | | 0.3945 | 0.4990 |
| **Rectal/pouch polyposis stratum** | n=11 | n=11 | n=12 |
| Subjects with any FAP-related event, n (%) | 4 (36.4) | 2 (18.2) | 5 (41.7) |
| Subject-years of follow up | 3.19 | 1.70 | 2.83 |
| FAP-related event per subject year | 10 | 15 | 6 |
| Subjects censored, n (%) | 7 (63.6) | 9 (81.8) | 7 (58.3) |
| Hazard ratio[a] (95% CI) | | 2.03 (0.4, 9.6) | 0.84 (0.2, 2.9) |

**Secondary Efficacy Endpoints**

Overall Investigator-Observed Change in Gastrointestinal Conditions by Month 12

Overall investigator observed change in gastrointestinal condition by Month 12 combined the investigator overall assessment scores at Month 6 and Month 12. No statistically significant differences between the combination treatment group and either single-agent treatment group were observed for LGIOI or UGIOI.

**Table 23: Analysis of UGIOI and LGIOI (ITT population)**

| | Combination N=56 | Sulindac N=58 | CPP-1X N=57 |
|---|---|---|---|
| UGIOI, n (%) | | | |
| Yes | 11 (19.6) | 10 (17.2) | 10 (17.5) |
| No | 45 (80.4) | 48 (82.8) | 47 (82.5) |
| p-value[a] | | 0.8127 | 0.8133 |
| LGIOI, n (%) | | | |
| Yes | 22 (39.3) | 22 (37.9) | 16 (28.1) |
| No | 34 (60.7) | 36 (62.1) | 41 (71.9) |
| p-value[a] | | >0.9999 | 0.2152 |

ITT=Intent-to-Treat; LGIOI=Lower Gastrointestinal Observed Improvement; UGIOI=Upper Gastrointestinal Observed Improvement

[a] p-value is from the exact Mantel-Haenszel for each of the 2 between-group comparisons stratified by randomization strata.

Overall Investigator Observed Change in Gastrointestinal Condition by End of Treatment

Overall investigator observed change in gastrointestinal condition was the cumulative gastrointestinal score from all visits using a scale (-2, -1, 0, +1, +2) that corresponded to the investigator's overall qualitative assessment of much worse, worse, no change, improved, much improved, respectively. This exploratory analysis excluded subjects without any postbaseline scores. Results for all subjects are provided in Table 24.

**Table 24: Analysis of cumulative gastrointestinal condition score at end of treatment (ITT population)**

| Analysis | n (%) Subjects UGIOI | | | n (%) Subjects LGIOI | | |
|---|---|---|---|---|---|---|
| Cumulative GI score category | Combination N=56 | Sulindac N=58 | CPP-1X N=57 | Combination N=56 | Sulindac N=58 | CPP-1X N=57 |
| Subjects with missing data | 8 (14.3) | 8 (13.8) | 5 (8.8) | 8 (14.3) | 10 (17.2) | 9 (15.8) |
| Score >0 | 15 (31.3) | 13 (26.0) | 13 (25.0) | 26 (54.2) | 22 (45.8) | 12 (25.0) |
| Score=0 | 19 (39.6) | 22 (44.0) | 32 (61.5) | 13 (27.1) | 20 (41.7) | 22 (45.8) |
| Score <0 | 14 (29.2) | 15 (30.0) | 7 (13.5) | 9 (18.8) | 6 (12.5) | 14 (29.2) |
| Overall GI condition[a] | | | | | | |
| Improved | 15 (31.3) | 13 (26.0) | 13 (25.0) | 26 (54.2) | 22 (45.8) | 12 (25.0) |
| Not improved | 33 (68.8) | 37 (74.0) | 39 (75.0) | 22 (45.8) | 26 (54.2) | 36 (75.0) |
| CMH test p-value[b] | | 0.5498 | 0.4509 | | 0.3944 | 0.0012 |
| Overall GI condition[c] | | | | | | |
| Stable or improved | 34 (70.8) | 35 (70.0) | 45 (86.5) | 39 (81.3) | 42 (87.5) | 34 (70.8) |
| Worsen | 14 (29.2) | 15 (30.0) | 7 (13.5) | 9 (18.8) | 6 (12.5) | 14 (29.2) |
| CMH test p-value[b] | | 0.9281 | 0.0601 | | 0.3954 | 0.1996 |

CMH=Cochran-Mantel-Haenszel; GI=gastrointestinal; ITT=Intent-to-Treat; LGIOI=Lower Gastrointestinal Observed Improvement; UGIOI=Upper Gastrointestinal Observed Improvement

[a] A subject's overall GI condition was improved if the cumulative score was >0, otherwise, the subject's overall condition was not improved from baseline.

[b] p-value is from the Mantel-Haenszel (general association) for each of the 2 between-group comparisons stratified by randomization strata.

[c] A subject's overall GI condition was considered stabled or improved if the cumulative score was ≥0, otherwise, the subject's overall condition was considered worsened from baseline.

### Health-Related Quality of Life

For this study, four instruments to measure HRQoL and patient preferences or utilities were administered to subjects at baseline and months 3, 6, 12, 18, 24, 30 36, 42, and 48. An end of treatment assessment was performed if the subject came off study at an interim timepoint. These instruments included the EORTC QLQ-C30, EORTC QLQ-CR29, EQ- 5D-5L, and a modified Cancer Worry Scale. HRQoL data was obtained while patients were receiving treatment.

**Table 25: Subjects with improvement or worsening in QLQ-C30 emotional functioning**

| Treatment Arm | N | # Improved | % Improved | # Worsened | % Worsened |
|---|---|---|---|---|---|
| Combination | 49 | 14 | 28.6% | 11 | 22.4% |
| Sulindac | 48 | 5 | 10.4% | 10 | 20.8% |
| CPP-1X | 51 | 7 | 13.7% | 8 | 15.7% |

## Ancillary analyses

Primary Efficacy Endpoint: Time to First FAP-Related Event

The following were considered in the exploratory analyses of the primary efficacy endpoint:

1. The SAP discussed 11 disease site subgroups to explore the subcategories of FAP-related events. In the final analysis, instead of performing exploratory analysis in each of the 11 disease site subgroups, combinations of those disease site subgroups and combinations of subcategories of FAP-related events were formed to explore and characterise the observed nominal benefit of combination therapy in the overall ITT Population.

2. 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 >/=10mm 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 stage progression). The following exploratory analyses were performed to assess the effect of excluding these 2 events from the composite endpoint.

1. Subjects with LGI Anatomy and FAP-Related LGI Events

Subjects with LGI anatomy were defined as all subjects with some intact LGI anatomy (i.e., subjects with an intact colon, rectum, and/or ileal pouch but excluding 13 subjects with a permanent ileostomy). Hence, a total of 158 ITT subjects were included in this disease site subgroup.

Time from Randomisation to First Occurrence of FAP-Related Events in subjects with LGI anatomy

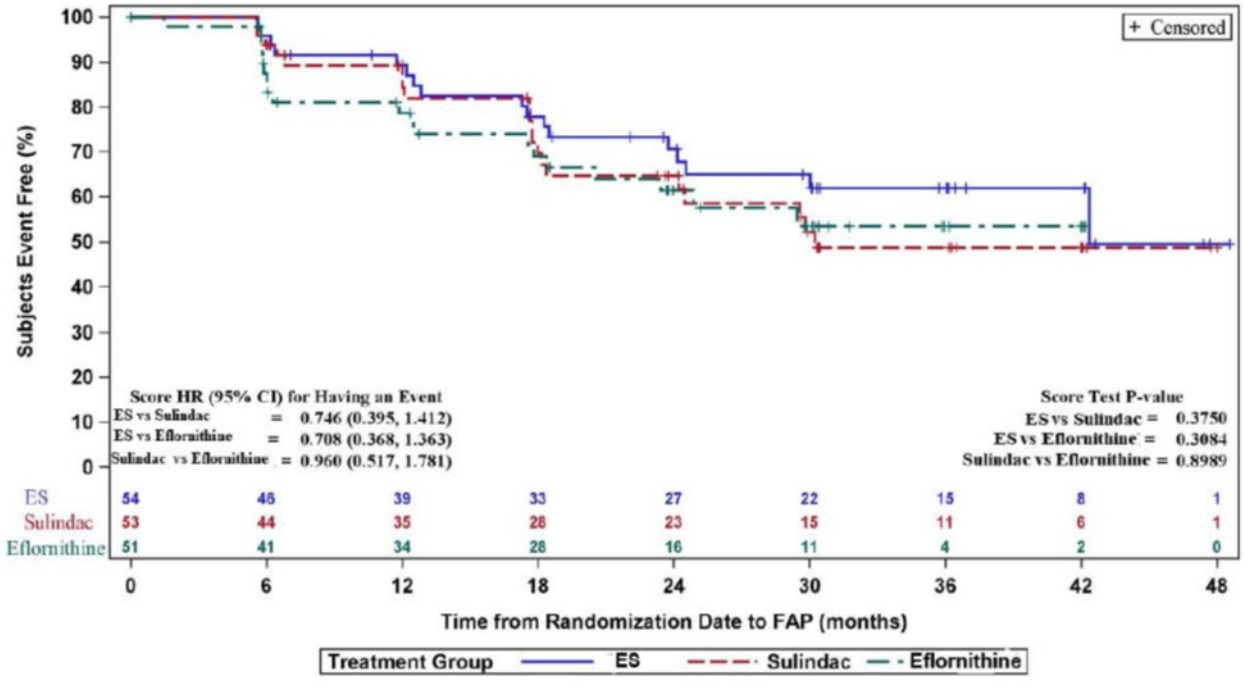



**Figure 11: Time from randomisation to first occurrence of FAP-related events in the ITT population excluding subjects with colectomy and ileostomy**

**Table 26: Time from randomisation to first occurrence of FAP-related events in the ITT population excluding subjects with colectomy and ileostomy**

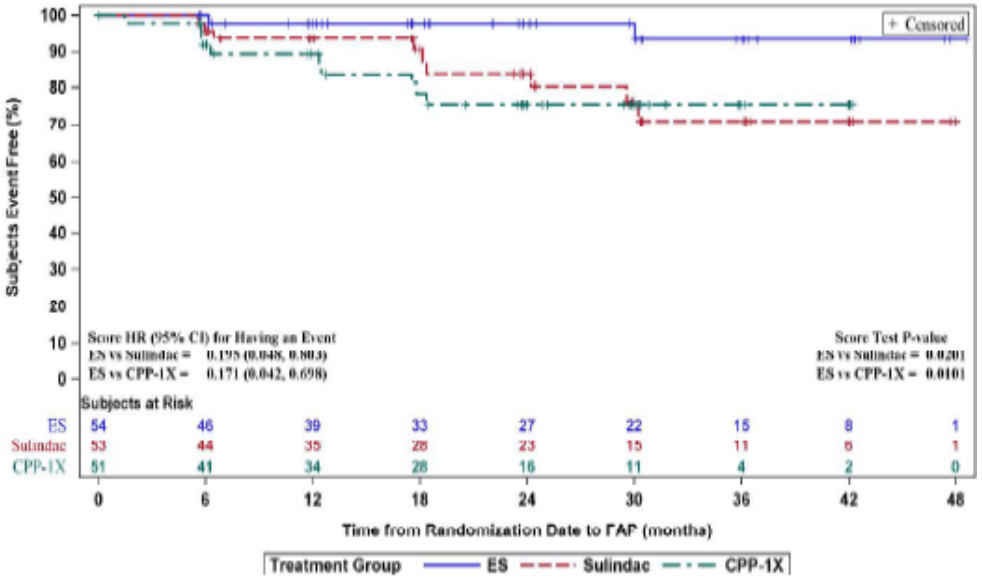
| Parameter = Time from Randomization Date to FAP (months) | | | | |
|---|---|---|---|---|
| **Analysis** | **Statistics** | **Eflornithine + Sulindac (N=54) (T1)** | **Placebo + Sulindac (N=53) (T2)** | **Eflornithine + Placebo (N=51) (T3)** |
| Subjects (%) | Subjects Event Free (Censored) | 37 (68.5%) | 33 (62.3%) | 32 (62.7%) |
| | Subjects Had Event | 17 (31.5%) | 20 (37.7%) | 19 (37.3%) |
| | | | | |
| KM Estimates | 25% tile KM Estimate (95% CI) | 18.46 (12.19, 30.03) | 17.74 (11.99, 24.21) | 12.48 (5.88, 23.43) |
| | 50% tile KM Estimate (95% CI) | 42.35 (24.54, NE) | 30.23 (18.37, NE) | NE (20.53, NE) |
| | 75% tile KM Estimate (95% CI) | NE (42.35, NE) | NE (NE, NE) | NE (NE, NE) |
| | KM Estimate Mean (SE) [1] | 32.42 (2.110)* | 23.78 (1.340)* | 22.26 (1.468)* |
| | | | | |
| Comparison: T1 vs (T2 or T3) | Score HR and 95% CL | | 0.746 (0.395, 1.412) | 0.708 (0.368, 1.363) |
| | Score P-value | | 0.3750 | 0.3084 |
| | | | | |
| [1] KM mean with sign of * indicates KM mean was restricted to L where L = maximum event time was less than the maximum censored time. | | | | |

2 analyses were performed to assess treatment effect on time to FAP-related LGI events.

<u>FAP-related LGI events included:</u>

1) Disease progression indicating need for colectomy with IRA or total proctocolectomy
2) Excisional intervention by surgical snare or trans-anal excision to remove any 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.
3) Disease progression indicating need for proctectomy
4) Disease progression indicating need for pouch resection
5) Development of cancer in rectum or pouch

A) Time from Randomisation to First Occurrence of All FAP-Related LGI Events




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

**Figure 12: Time from randomisation to first occurrence of any FAP-related LGI event in subjects with LGI anatomy (ITT population excluding subjects with colectomy and ileostomy)**

**Table 27: Analysis of time from randomisation to first occurrence of any FAP-related LGI event (ITT population excluding subjects with colectomy and ileostomy)**

| | Combination N=54 | Sulindac N=53 | CPP-1X N=51 |
|---|---|---|---|
| Subjects with any FAP-related event, n (%) | 2 (3.7) | 9 (17.0) | 10 (19.6) |
| Subjects censored, n (%) | 52 (96.3) | 44 (83.0) | 41 (80.4) |
| Hazard ratio[a] (95% CI) | | 0.20 (0.0, 0.8) | 0.17 (0.0, 0.7) |
| p-value[b] | | 0.0201 | 0.0101 |

CI=confidence interval; FAP=familial adenomatous polyposis; ITT=Intent-to-Treat; LGI=lower gastrointestinal
Note: Time to event is defined as (date of event or censored date −randomization date + 1). Month is defined as 30.4375 days.

[a] Hazard ratio of probability of having an event was derived from the Cox proportional hazards model.

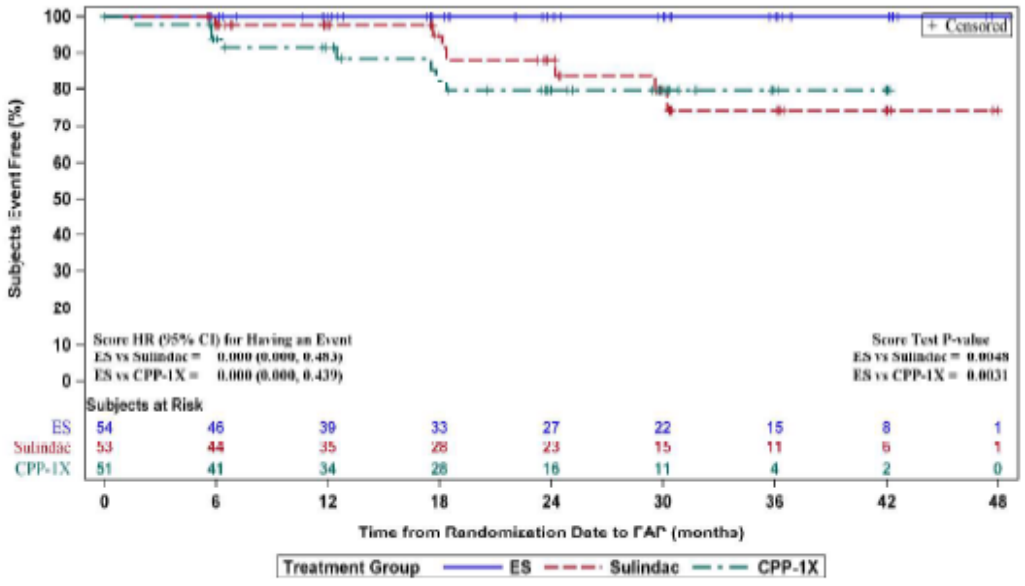
[b] The hazard ratio 95% CI for each treatment group and the p-value for the between groups comparisons were derived from the stratified Cox proportional hazards model using the score method; an external SAS macro hazard ratio developed based on Lin DY et al.[61] was used to implement this analysis method.

**Table 28: Analysis of time from randomisation to first occurrence of FAP-related lower GI event (months - ITT population)**

| Analysis | Statistics | CPP-1X + Sulindac (N=56) (T1) | CPP-1X (Placebo) + Sulindac (N=58) (T2) | CPP-1X + Sulindac (Placebo) (N=57) (T3) |
|---|---|---|---|---|
| Subjects (%) | Subjects Event Free (Censored) | 54 (96.4%) | 49 (84.5%) | 47 (82.5%) |
| | Subjects Had Event | 2 (3.6%) | 9 (15.5%) | 10 (17.5%) |
| KM Estimates | 25% tile KM Estimate (95% CI) | NE (NE, NE) | 30.23 (18.14, NE) | NE (12.48, NE) |
| | 50% tile KM Estimate (95% CI) | NE (NE, NE) | NE (NE, NE) | NE (NE, NE) |
| | 75% tile KM Estimate (95% CI) | NE (NE, NE) | NE (NE, NE) | NE (NE, NE) |
| | KM Estimate Mean (SE) [1] | 29.53 (0.695)* | 27.41 (1.059)* | 16.78 (0.593)* |
| Comparison: T1 vs (T2 or T3) | Score HR and 95% CL [2] | | 0.218 (0.053, 0.901) | 0.193 (0.047, 0.790) |
| | Score P-value | | 0.0332 | 0.0187 |

[1] KM mean with sign of * indicates KM mean was restricted to L where L = maximum event time was less than the maximum censored time.
[2] Cox proportional hazards analysis on probability of having an event

B) Time to FAP related LGI events Censoring Events involving excision of >/=10mm polyps




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

**Figure 13: Time from randomisation to first occurrence of any FAP-related LGI event censoring ≥ 10 mm polyps if occurred alone (ITT population excluding subjects with colectomy and ileostomy)**

**Table 29: Analysis of time from randomisation to first occurrence of any FAP-related LGI event censoring ≥ 10 mm polyps if occurred alone (ITT population excluding subjects with colectomy and ileostomy)**

| | Combination N=54 | Sulindac N=53 | CPP-1X N=51 |
|---|---|---|---|
| Subjects with any FAP-related event, n (%) | 0 | 7 (13.2) | 8 (15.7) |
| Subjects censored, n (%) | 54 (100.0) | 46 (86.8) | 43 (84.3) |
| Hazard ratio[a] (95% CI) | | 0.000 (0.000, 0.483) | 0.000 (0.000, 0.439) |
| p-value[b] | | 0.0048 | 0.0031 |

CI=confidence interval; FAP=familial adenomatous polyposis; ITT=Intent-to-Treat; LGI=lower gastrointestinal
Note: Time to event is defined as (date of event or censored date – randomization date + 1). Month is defined as 30.4375 days.

[a] Hazard ratio of probability of having an event was derived from the Cox proportional hazards model stratified by randomization strata.

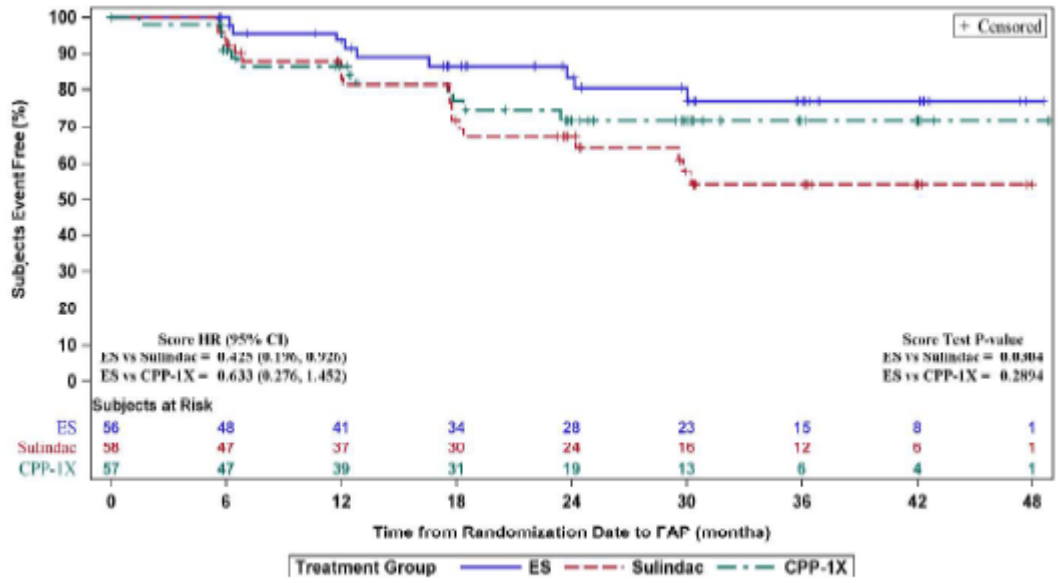
[b] The hazard ratio 95% CI for each treatment group and the p-value for the between groups comparisons were derived from the stratified Cox proportional hazards model using the score method; an external SAS macro hazard ratio developed based on Lin DY et al.[61] was used to implement this analysis method.

2. Exploratory Analyses Censoring Events Involving Spigelman Stage Progression

Prior to the initiation of this study, there was concern that Spigelman stage progression may not be an optimal measure of assessing the need for or actual surgeries in the UGI tract. Thirty of the 63 FAP-related events in this study were classified as Spigelman stage progression. Only 8 of these 30 events also had an associated need for or actual surgical procedures. For the other 22 cases, Spigelman stage progression was not associated with any clinically meaningful consequence.

A) ITT Population: Censoring the 22 Subjects with Spigelman Stage Progression

In this exploratory analysis, 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.

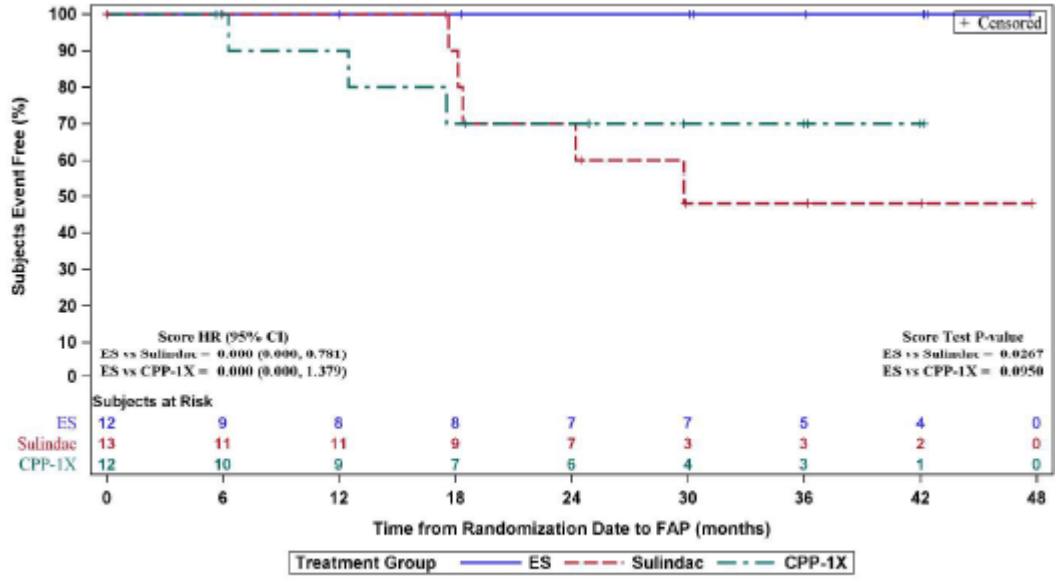



CI=confidence interval; ES=CPP-1X (eflornithine) + sulindac; FAP=familial adenomatous polyposis; HR=hazard ratio; ITT=Intent-to-Treat

**Figure 14: Time from randomisation to first occurrence of any FAP-related event (ITT population censoring 22 subjects with Spigelman stage progression alone without any Spigelman stage progression related surgeries)**

B) Pre-Colectomy Stratum: Censoring Events Involving Spigelman Stage Progression

In this exploratory analysis of the primary endpoint that censored Spigelman stage progression events among subjects in the pre-colectomy stratum, the percentage of 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 (p=0.0267) for the combination vs. sulindac and 0.000 (p=0.0950) for the combination vs. CPP-1X.

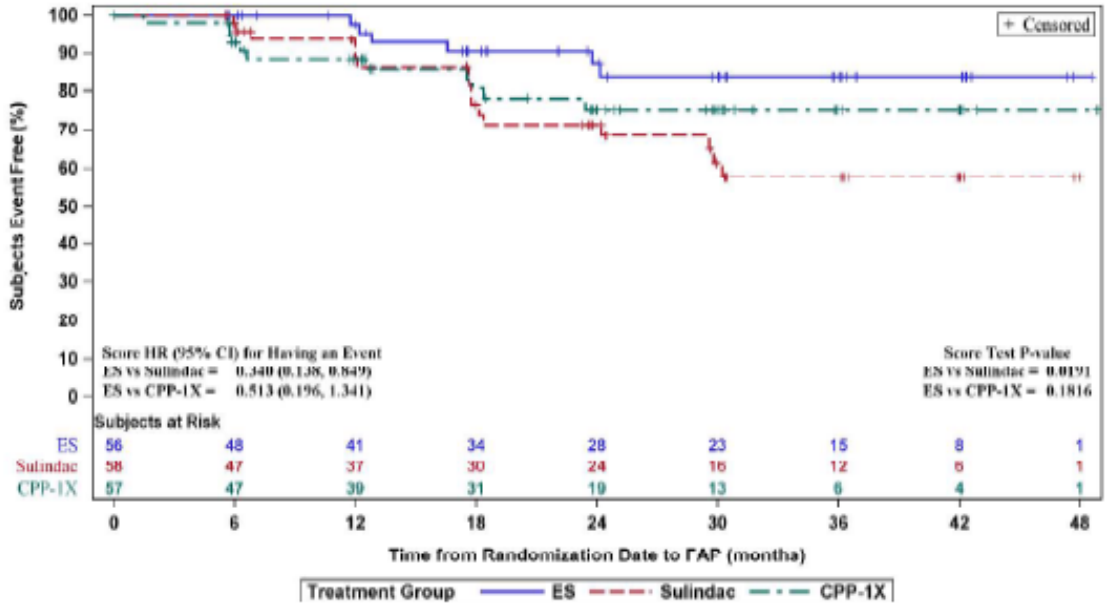



CI=confidence interval; ES=CPP-1X (eflornithine) + sulindac; FAP=familial adenomatous polyposis; HR=hazard ratio; ITT=Intent-to-Treat

**Figure 15: Time from randomisation 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**

3. Censoring Events Involving Spigelman Stage Progression and Excision of ≥ 10mm Polyps

In a post hoc 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 >/=10mm 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.




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

**Figure 16: Time from randomisation to first occurrence of any FAP-related event (ITT population censoring excision of ≥ 10 mm polyps and Spigelman stage progression if occurred alone)**

**Table 30: Analysis of time from randomisation to first occurrence of any FAP-related event (ITT population censoring excision of ≥ 10 mm polyps and Spigelman stage progression if occurred alone)**

| | Combination N=56 | Sulindac N=58 | CPP-1X N=57 |
|---|---|---|---|
| Subjects with any FAP-related event, n (%) | 6 (10.7) | 16 (27.6) | 11 (19.3) |
| Subjects censored, n (%) | 50 (89.3) | 42 (72.4) | 46 (80.7) |
| Hazard ratio[a] (95% CI) | | 0.34 (0.1, 0.8) | 0.51 (0.2, 1.3) |
| p-value[b] | | 0.0191 | 0.1816 |

CI=confidence interval; FAP=familial adenomatous polyposis; ITT=Intent-to-Treat

[a] Hazard ratio of probability of having an event was derived from the Cox proportional hazards model stratified by randomization strata.

[b] The hazard ratio 95% CI for each treatment group and the p-value for the between groups comparisons were derived from the stratified Cox proportional hazards model using the score method; an external SAS macro hazard ratio developed based on Lin DY et al.[61] was used to implement this analysis method.

## Summary of main study

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 31: Summary of efficacy for trial CPP FAP-310**

| | | | | | |
|---|---|---|---|---|---|
| **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) | | | | | |
| Study identifier | CPP FAP-310, 2012-000427-41, NCT01483144 | | | | |
| Design | Randomised, blinded, multicentre study, parallel assignment | | | | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | | 24- 48 months<br>not applicable<br>not applicable | | |
| Hypothesis | Superiority | | | | |
| Treatments groups | Eflornithine + Sulindac (ES Coadministered) | | Eflornithine 750 mg + sulindac 150 mg, mean duration 23.7 (13.96) months, 56 randomised | | |
| | Eflornithine + placebo (Eflornithine) | | Eflornithine 750 mg + sulindac placebo mean duration 2320.5(12.24) months, 57 randomised | | |
| | Sulindac + placebo (Sulindac) | | Eflornithine placebo + sulindac 150 mg, mean duration 21.2 (13.44) months 58 randomised | | |
| Endpoints and definitions | Primary endpoint | Time to Event | Time to FAP-related event. FAP related events included disease progression indicating the need for surgical intervention, Spigelman stage progression, development of advanced adenomas in the rectum or surgical pouch, cancer, or death. | | |
| | Secondary Outcome | Pre-colectomy | Time to FAP-related event by disease site stratification | | |
| | | LGI | Time to FAP-related event in the lower GI anatomy | | |
| | | Pre-colectomy | Time to FAP-related event in the pre-colectomy stratum, censoring Spigelman stage progression without need surgery or other FAP-related event | | |
| Database lock | 08-Mar-2019 | | | | |
| **Results and Analysis** | | | | | |
| **Analysis description** | **Primary Analysis** | | | | |
| Analysis population and time point description | Intent to treat<br>Time to Event (up to 48 months) | | | | |
| Descriptive statistics and estimate variability | Treatment group | ES Coadministered | Sulindac | Eflornithine | |
| | Number of subjects | 56 | 58 | 57 | |
| | Subjects with any FAP-related event, n (%) | 18 (32.1) | 22 (37.9) | 23 (40.4) | |
| | Subjects censored, n (%) | 38 (67.9) | 36 (62.1) | 34 (59.6) | |
| Effect estimate per comparison | Primary endpoint | Comparison groups | ES Coadministered versus Sulindac | | |
| | | Hazard Ratio | 0.71 | | |
| | | 95% Confidence Interval | (0.4, 1.3) | | |
| | | P-value using stratified Cox proportional hazards model using the score method | 0.2898 | | |
| | Primary endpoint | Comparison groups | ES Coadministered versus Eflornithine | | |

| | | | | |
|---|---|---|---|---|
| | | Hazard Ratio | | 0.66 |
| | | 95% Confidence Interval | | (0.36, 1.24) |
| | | P-value using stratified Cox proportional hazards model using the score method | | 0.2001 |
| **Analysis description** | | **Secondary endpoint** | | |
| Analysis population and Endpoint | | Intent to treat<br>Upper and Lower Gastro Intestinal Observed Improvement | | |
| Descriptive statistics and estimate variability | Treatment group | ES Coadministered | Sulindac | Eflornithine |
| | Number of subjects | 56 | 58 | 57 |
| | UGIOI Yes, n (%) | 11 (19.6) | 10 (17.2) | 10 (17.5) |
| | UGIOI No, n (%) | 45 (80.4) | 48 (82.8) | 47 (82.5) |
| | P-value | | 0.8127 | 0.8133 |
| | LGIOI Yes, n (%) | 22 (39.3) | 22 (37.9) | 16 (28.1) |
| | LGIOI No, n (%) | 34 (60.7) | 36 (62.1) | 41 (71.9) |
| | P-value | | >0.9999 | 0.2152 |
| Analysis population and Endpoint | | Population?<br>Subjects with improvement or worsening in QLQ-C30 emotional functioning | | |
| Descriptive statistics and estimate variability | Treatment group | ES Coadministered | Sulindac | Eflornithine |
| | Number of subjects | 49 | 48 | 51 |
| | Improved, n (%) | 14 (28.6) | 5 (10.4) | 7 (13.7) |
| | Worsened, n (%) | 11 (22.4) | 10 (20.8) | 8 (15.7) |
| Notes | Reasons for not completing the study included adverse events (11.1%), protocol violation (5.3%), withdrew consent (4.1%), lost to follow-up (4.1%), and physician decision (0.6%) | | | |

## Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

## Clinical studies in special populations

**Table 32: Summary of elderly populations treated with Eflornithine or the combination of eflornithine and sulindac**

| | Trial Name | Age 65-74 (Older subject number /total number) | Age 75-84 (Older subject number /total number) | Age 85+ (Older subject number /total number) |
|---|---|---|---|---|
| # Subjects exposed to eflornithine/ sulindac combination | CPP FAP-310 | 1/56 | 0/56 | 0/56 |
| | PSCA | 54/188 | 10/188 | 0/188 |
| | CPP-P6-366 | 0/23 | 0/23 | 0/23 |
| | CPP-P9-658 | 0/12 | 0/12 | 0/12 |
| # Subjects exposed to eflornithine | ELA-P4-466 | 6/32 | 1/32 | 0/32 |
| | CPP FAP-310 | 4/56 | 0/56 | 0/56 |

## *Supportive study*

**Pharmacoprevention of Sporadic Colorectal Adenomas (PSCA) Study**

***Phase IIB****: "A Phase II Clinical Trial of a Randomized, Double-Blind, Placebo- Controlled Clinical Trial of DFMO (Difluoromethlyornithine) and Sulindac against Various Endpoints of Colorectal Pathobiology in a Cohort of Individuals at Increased Risk of Colorectal Carcinoma*" N01-CN-75019

***Phase III:*** *"A Phase III Randomized, Double-Blind, Placebo-Controlled Clinical Trial of the Combination of DFMO and Sulindac to Decrease the Rate of Recurrence of Adenomatous Polyps in the Colon"*
R01-CA-88078

The PSCA Study was a placebo-controlled trial to evaluate the efficacy and safety of the combination treatment in a cohort of patients at increased risk of colorectal carcinoma and adenomatous polyps in the colon. This study measured number (%) of subjects with adenoma after treatment as the primary efficacy endpoint after randomisation. The study was conducted by the University of California – Irvine with grants from the National Cancer Institute and ran from 1998 to 2008. The primary data was published in 2008 (Meyskens et al. 2008). The final version of the clinical study report was submitted to the National Cancer Institute in 2012.

When the phase IIB randomised trial began, there was insufficient funding to utilise colon polyps as the endpoint. After successfully obtaining funding, the phase IIB investigation was converted to a placebo-controlled, randomised, double-blind phase III trial with recurrence of all adenomas as the primary endpoint.

To facilitate consideration of the study as a supportive trial in support of filing an NDA with the U.S. FDA, Cancer Prevention Pharmaceuticals (CPP) obtained Right of Reference from the University of California – Irvine in order to obtain patient-level data requested by the FDA at the pre-NDA meeting. In reviewing the PSCA clinical study report, CPP noted that the analysis of the data in the clinical study report was not done in accordance with current pharmaceutical industry standards. The PSCA study had three important potential issues based on the current pharmaceutical industry research standard, namely:

1) The efficacy analysis was not performed for the Intent-to-Treat (ITT) population

2) Missing data assessment was planned but not performed

3) Type I error was not adjusted for interim analyses

The Statistical Analysis Plan (SAP) outlined the statistical methodologies to be used for analysis of efficacy for the PSCA Study to address the three identified issues. The analyses results identified in the SAP were the basis for the new clinical study report, identified as CAT-001 (see further below).

The original PSCA Study was terminated early based on the recommendation of the Data Monitoring Committee (due to an interim analysis that demonstrated efficacy and concerns based on safety findings of other NSAID studies at the time).

Methods

The study was executed as a randomised, double-blind investigation of DFMO and Sulindac against a concurrent double placebo. Participants were chosen who had an adenoma ≥ 3 mm, demonstrated within 5 years prior to enrolment and had a colonoscopy performed within 6 months of entry to trial. A one-month run-in period was an integral part of the design to assist in eliminating participants with insufficient compliance. The dose of DFMO had been chosen based on earlier Phase IIA and IIB trials with the chosen dose of sulindac at approximately 50% of the daily dose in use for arthritis and other conditions. Participants could have a prior history of ≤ 10 days/month NSAID use and those who were taking baby aspirin (81 mg daily or 325 mg twice a week) were eligible for study entry. Stratification did occur based upon ASA usage, in order to determine if any difference of effect occurred between these groups. 36 months was selected as the duration of treatment because approximately 50% of individuals aged 60 (the average age of participants in our trial) will develop adenomas within 3 years.

Study participants

Participants must have undergone baseline colonoscopy with adequate rectal mucosal sampling and polypectomies. In those having adequate documentation of this procedure within the last six months, they must have undergone baseline flexible sigmoidoscopy with adequate rectal mucosal sampling.

To undergo pre-randomisation screening procedures:

a. Age 40-80 years with a history of >1 resected adenoma >3mm within 5 years from entry.

b. No history of invasive cancer within 5 years, excepting those with adequately treated non melanomatous skin cancer, Stage I cervical cancer, Duke's A colon cancer, or CLL (Stage 0).

c. No severe metabolic disorders or other significant acute or chronic diseases, including kidney disease (serum creatinine must be <1.5mg/dl and UA must have <1+protein, 0-3 casts, 0-5 WBCs and RBCs), liver disease (serum Bilirubin must be <2.0mg/dl, AST and ALT must be <2x normal), chronic anaemia (HCT must be >35 volume%,) leukopenia (WBC must be >4,000), thrombocytopenia (platelets must be >100,000), or within the approved reference range of the certified laboratory performing the site specific analysis.

d. No anticipated radiation or chemotherapy.

e. No personal OR family history of familial adenomatous polyposis.

f. No special dietary requirements or additives. Not consuming a diet that will preclude taking the study medications.

g. No concomitant use of calcium supplements (up to 520mg/day will be allowed), corticosteroids, nonsteroidal anti-inflammatories, nor anticoagulants on a regular or predictable intermittent basis. (Up to 81mg ASA, orally, every day [or up to 325 mg twice per week] is allowed for CV prophylaxis).

h. No history of abnormal wound healing or repair, or conditions that predispose to the same.

i. SWOG PS <1.

j. Anticipated regional stability over the next 36 months.

k. No personal history of colon resection of >40cm or resection of inflammatory bowel disease.

l. Pregnant or lactating women are not eligible. Premenopausal and perimenopausal women must be using adequate birth control methods.

m. Must give informed consent approval by the local Human Subjects Committee.

n. No history of allergies to NSAIDs or DFMO.

o. No documented history of gastric/duodenal ulcer within the last 12 months. Not currently being treated for gastric/duodenal ulcer or experiencing symptoms at study entry.

For randomisation to agents (based upon results of pre-randomisation screening):

a. Must continue to meet eligibility criteria "for pre-randomisation screening" following baseline medical history, physical examination, and baseline laboratory evaluations (CBC, Metabolic Panel to include liver function tests, bun, and creatinine, UA w/micro, compliance with run-in medication).

b. Must have acceptable audiometry evaluation (<20dB loss for age, at any frequency).

c. Must undergo baseline colonoscopy with adequate rectal mucosal sampling and polypectomies (or in those having adequate documentation of this procedure within the last six months, undergo baseline flexible sigmoidoscopy with adequate rectal mucosal sampling).

Removal of participants from therapy or assessment

1) Failure to complete scheduled rectal biopsies. Participants were given up to 13 months to complete the 12 month measurements, and up to 39 months to complete the 36 month measurement.

2) Unacceptable toxicity.

3) Refusal or inability of participant to continue the study.

4) Development of an invasive malignancy or serious illness which is considered by the participant's own physician and/or the project physician to prevent further participation.

In 2005, the DSMB recommended the implementation of a 6 month follow-up audiology exam.

In all cases of early termination listed above (with the exception of refusal to continue), if a participant had completed ≥ 12 months on treatment, he/she was asked to return for this exam. Evidence of "poor" compliance (< 50% project intake) was not criteria for removal from the study, as analysis was done on an "intent to treat" basis with drug treatment.

Treatments

During the first month of the study, the run-in period, all participants were administered the reference therapy, placebos for both DFMO and Sulindac. For the duration of the study, 36 months, the treatment arm was administered DFMO and Sulindac, while the placebo arm received the reference therapy.

**Table 33: Treatments used in PSCA study**

| **STUDY AGENTS (Phase IIB)** | Formulation | Dose | Regimen | Route |
|---|---|---|---|---|
| Sulindac | Tablets | 150mg | Daily | P.O. |
| Difluoromethylornithine (DFMO) | Solution | 0.20Gm/$m^2$ | Daily | P.O. |
| OR | | | | |
| Difluoromethylornithine (DFMO) | Tablets | 500 mg | Daily | P.O. |
| **STUDY AGENTS (Phase III)** | | | | |
| Sulindac | Tablet | 150mg | QD | P.O. |
| Difluoromethylornithine (DFMO) | Tablet | 250mg | II QD | P.O. |
| **REFERENCE THERAPY (Phase IIB)** | Formulation | Dose | Regimen | Route |
| Sulindac Placebo | Tablets | -- | Daily | P.O. |
| DFMO Placebo | Solution | -- | Daily | P.O. |
| OR | | | | |
| DFMO Placebo | Tablets | -- | Daily | P.O. |
| **REFERENCE THERAPY (Phase III)** | | | | |
| Sulindac Placebo | Tablet | 1 | QD | P.O. |
| DFMO Placebo | Tablet | 1 | II QD | P.O. |

All participants maintained a 500 mg dose of DFMO and a 150 mg dose of Sulindac throughout the 36 months on treatment. The dose of DFMO, 500 mg (2 tablets QD) was chosen based on Phase IIA and IIB dose de-escalation trials.

Prior and Concomitant Therapy:

Participants could have a prior history of ≤ 10 days/month NSAID use and those who were taking aspirin (81 mg daily or 325 mg twice a week for CV prophylaxis) were eligible for study entry and could continue their use of ASA. As participants were stratified for ASA usage, effects of aspirin on study outcome would be ascertained from this stratified data.

For Phase IIB and III, concomitant use of corticosteroids, nonsteroidal anti-inflammatories or anticoagulants (on a regular or predictable intermittent basis) was not allowed. Additionally no concomitant use of calcium supplements (> 520mg/day) was allowed for participants on Phase IIB but Phase III participants were allowed use of calcium supplements (up to 1000 mg/day). No significant effect of calcium intake was anticipated, however as with all medications, its usage was recorded.

Use of all concomitant medications was recorded at study entry and at each subsequent visit for the duration of the study.

Objectives

1. To conduct a randomised, double-blind placebo-controlled phase III clinical chemoprevention trial of the combination of DFMO plus sulindac to decrease the rate of new adenomatous polyp formation. Hypothesis: This combination of candidate chemoprevention agents will lower the rate of adenomatous polyps by 50% or greater**.**
2. To correlate the effects of the combination on polyamine and prostaglandin contents in the flat mucosa to the rate of adenoma formation. The changes in the levels of these biochemical parameters will also be used as one measure of compliance as well as an indication that the agent is producing the intended biochemical modulation.
4. Hypothesis: The level of reduction of polyamine and prostaglandin contents of flat mucosa after 36 months of treatment will be correlated with the rate of adenoma recurrence.

3. To determine the rate of side effects in patients randomised to the combination therapy over the course of the intervention.

Hypothesis: Both GI and non-GI side effects, as well as drop-offs after randomisation, will be no different between the treatment and placebo arms.

Outcomes/endpoints

The specific efficacy endpoints for the IIB and III studies included the correlation between measurements of polyamines in rectal mucosa as SEBs and recurrence of polyps. Recurrence of colorectal adenomas, as assessed by the colonoscopic exam and pathology report, with incidence and size of adenomas and carcinomas were measured. This marker is a well-established indicator for risk for colorectal cancer. The incidence of adenomas was recorded from each participant's qualifying colonoscopy report upon study entry. Data concerning the recurrence of adenomas was collected when each participant completed his/her end-of- study colonoscopy. The end-of-study colonoscopy was scheduled to occur after 36 months on treatment, ± 3 months.

Surrogate endpoint biomarkers from adenomatous tissue and rectal mucosal tissue including crypt/cellular/nuclear morphometry, polyamine and prostaglandin content, and assessment of proliferative (Ki67), uninduced apoptosis and preneoplastic (CEA, sialyl-TN, p53, bcl-2) features were also examined. SEBs were measured at baseline and at 12 and 36 months after beginning treatment. (For phase III participants, these biomarkers were only be measured at baseline and 36 months.)

Measurements of surrogate endpoint biomarkers, including but not limited to Ki-67, CEA, p53 and bcl-2; of prostaglandins and PGE2; as well as recurrence of adenomatous polyps were the primary efficacy and intermediate endpoint variables used to determine efficacy of the combination of DFMO/sulindac.

Sample Size

In addition to a Vanguard cohort of an expected 200 evaluable participants from the phase IIB trial, it was calculated that a total of 124 randomised Second Cohort subjects should be entered into the phase III trial to assure 92 additional evaluable participants.

The primary outcome variable for this study will be recurrence of adenoma. The original sample size calculations were based on a Fisher's Exact Test for comparison of the treatment groups with regard to the proportion of participants developing at least one adenoma between placebo and treatment groups

The rationale of the sample size for the combined phase IIb/III study was (a) having 146 subjects in each arm, (b) the rate of polyp development by month 36 in placebo controls ranges from 20-35%, (c) the effect of DFMO plus Sulindac is a 40% to 60% reduction, and (d) the significance level is 5%, then the statistical power of detecting a treatment difference based on Fisher's exact test is shown in Table 34. If the incidence of interval incident adenomas in placebo controls is 30 – 35%, 146 participants in each group will be sufficient to detect a reduction from the placebo rate of at least 50% with a power of at least 0.84. For a placebo rate of 20-35%, a reduction from the placebo rate of at least 60% appears to be detectable with a power of at least 0.81.

**Table 34: Power for detection of 50-60% reduction from the placebo proportion with polyps**

| Placebo Proportion with Polyps | 50% Reduction | 60% Reduction |
|---|---|---|
| 35% | 0.91 | 0.98 |
| 30% | 0.84 | 0.96 |
| 25% | 0.74 | 0.90 |
| 20% | 0.61 | 0.81 |

The maximal sample size was recalculated in March 2005 based on pooled data from N=145 evaluable patients, with no change to the total planned trial enrolment. For the purposes of sample size recalculation, data on the recurrence rate of all 145 evaluable participants were used. The incidence of adenoma recurrence in the combined treatment groups observed thus far was 24.14% (35/145). The minimum follow-up time prior to colonoscopy on these participants was 20 months, with a maximal follow-up time of 54 months. Seven (7) participants underwent colonoscopy at less than 30 months of follow-up, while 3 participants underwent colonoscopy at greater than 42 months of follow-up. Sample size calculations were based on the two sample tests of binomial proportions, rather than Fisher's exact test as originally specified in the protocol. The planned enrolment of 146 patients per arm was estimated to provide 89.48% power to detect a 50% decrease the rate of adenoma recurrence.

Randomisation and Blinding

Participants who successfully completed the 4-week run-in and who took placebo medication on at least 5 of 7 days each week (by volume and pill measurements/count) were eligible for randomisation and continuation. Non-compliant participants were dropped prior to randomisation. Compliant subjects were randomly assigned to one of two treatment groups: placebo or combination of drugs. Randomisation was in fixed blocks of 8, 4 subjects assigned to the treatment group and 4 subjects assigned to the placebo group. Treatment groups were assigned randomly by the Biostatistics Group at UC Irvine using telephone registration. Only the Biostatistics Group had access to the uncoded list of participant names, treatment code, and treatment identity. Thus, once active treatment was started, the study was double-blind. A sealed envelope is maintained in the participant study file with treatment assignment in case a clinical emergency necessitated immediate information. Opening of this code information would cause the participant to be removed from treatment, but remain on study for further assessment of toxicities, polyp recurrence and other endpoints (when possible). Randomised participants were stratified by study site and ASA usage.

Statistical Methods

The primary endpoint was to be analysed in a modified ITT population who had at least 1 dose of study drug and who had $\geq$ 1 post treatment colonoscopy.

Fisher's exact test was to be used to compare treatment groups with regard to the proportions of participants with at least one new adenoma. 95% CIs for the proportion of recurrent adenomas will be computed for each treatment group. For multivariable analyses, logistic regression was to be used to model the presence of at least one adenoma. Odds ratios for development of at least one new adenoma and 95% CIs for the odds ratios were to be computed for predictor variables included in the models.

However, risk ratios for the development of at least one new adenoma based on log-binomial regressions with adjustment for covariates and associated 95% CIs are instead presented in the PSCA CSR.

**Results from PSCA**

Participant flow

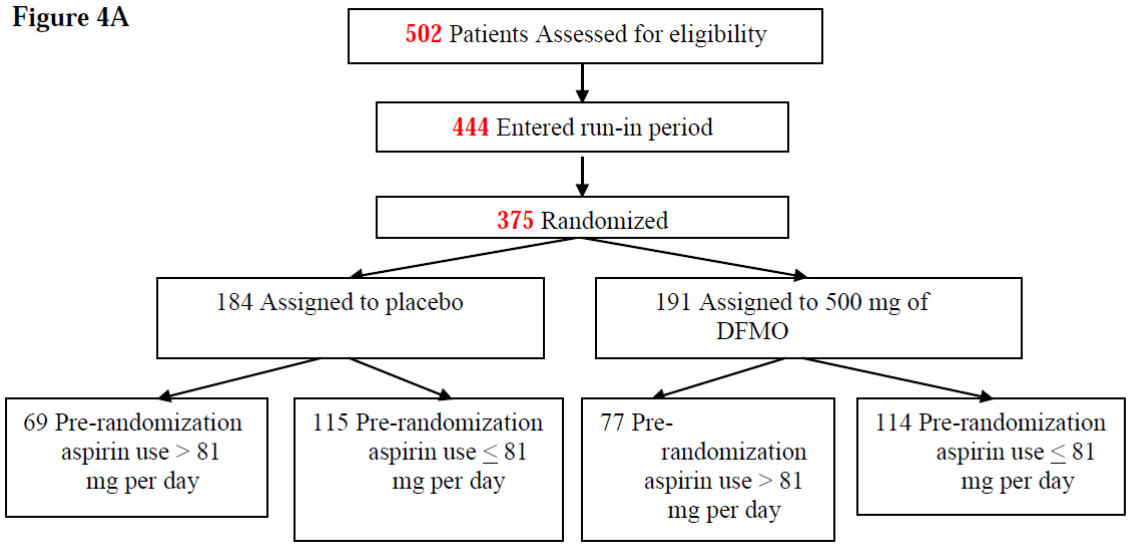



**Figure 17: Disposition of subjects**

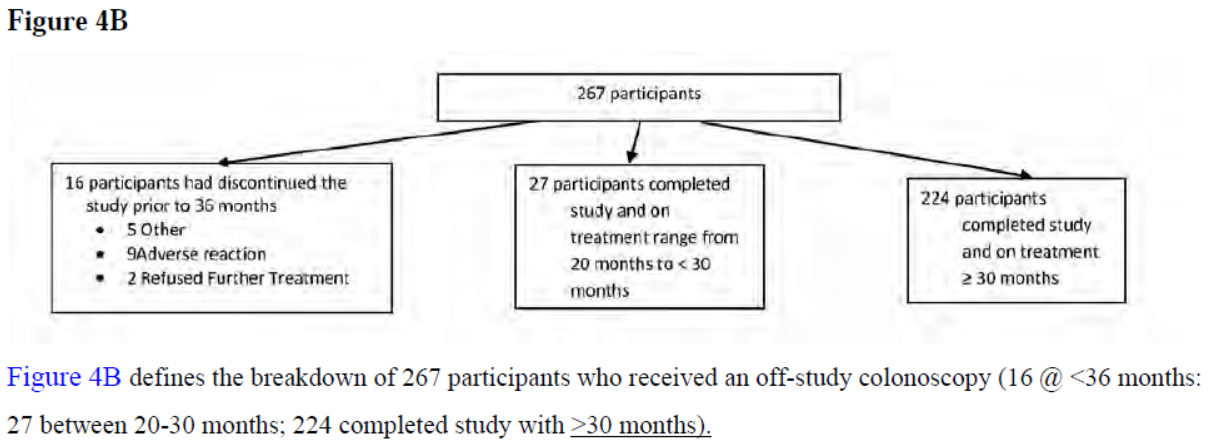



Figure 4B defines the breakdown of 267 participants who received an off-study colonoscopy (16 @ <36 months: 27 between 20-30 months; 224 completed study with ≥30 months).

**Figure 18: Breakdown of participants who received an off-study colonoscopy**

Recruitment

The study was conducted at 11 sites in the US.

Phase IIB trial first patient enrolled: July 13, 1998

Phase III trial first patient enrolled: November 22, 2002

Phase IIB last patient completed: October 3, 2005

Phase III last patient completed August 29, 2008

Conduct of Study

The initial investigation was structured as a randomised phase IIB study in which a variety of markers were to be correlated with adenoma recurrence. The investigation was subsequently converted into a full

phase III randomised trial in which adenomas were the primary endpoint. Additionally, upon recommendation of the DSMB, 18-month audiograms and 42-month (6 months off-treatment) audiograms were instituted in addition to the previously planned baseline and 36 month visits.

Formation of Stopping Rules: In March of 2005, potential stopping rules for efficacy and futility were formulated and presented to the external Data and Safety Monitoring Board for the Phase III clinical trial of Sulindac and DFMO combination. It was agreed that an interim analysis plan using a O'Brien-Fleming efficacy bound with a futility bound corresponding to P=0.9 in the unified family of group sequential designs (Kittelson JM, Emerson SS. A unifying family of group sequential test designs. Biometrics 1999; 55:874-82) would be instituted. The Data and Safety Monitoring Board recommended conduct of two early interim analyses, occurring at 60% and 80% of the maximal planned information for the trial. As previously described, the maximal sample size was also recalculated based on pooled adenoma incidence data, with no change to total planned trial enrolment.

Baseline data

**Table 35: Participant information detailing the number and sex of IIb and III that were entered into the trial and what stage of completion was obtained**

| | Phase | | | |
|---|---|---|---|---|
| | IIb (N = 246) | | III (N = 129) | |
| | DFMO/Sulindac (N = 128) | Placebo (N = 118) | DFMO/Sulindac (N = 63) | Placebo (N = 66) |
| **Gender** | | | | |
| Male | 103 (80%) | 89 (75%) | 44 (70%) | 49 (74%) |
| Female | 25 (20%) | 29 (25%) | 19 (30%) | 17 (26%) |
| **Completed Study** | 93 (73%) | 78 (66%) | 38 (60%) | 43 (65%) |
| On treatment ≥ 36-month | **58** | **53** | **11** | **19** |
| Male | 52 | 36 | 8 | 11 |
| Female | 6 | 17 | 3 | 8 |
| 30-month ≤ On treatment < 36-month | **35** | **25** | **15** | **7** |
| Male | 26 | 22 | 12 | 6 |
| Female | 9 | 3 | 3 | 1 |
| 24-month ≤ On treatment < 30-month | **0** | **0** | **10** | **13** |
| Male | 0 | 0 | 5 | 12 |
| Female | 0 | 0 | 5 | 1 |
| 18-month ≤ On treatment < 24-month | **0** | **0** | **2** | **4** |
| Male | 0 | 0 | 1 | 4 |
| Female | 0 | 0 | 1 | 0 |

**Table 36: Baseline characteristics of the participants**

| | All Randomized Subjects | | Randomized Subjects in the efficacy analysis cohort | |
|---|---|---|---|---|
| | Placebo (N = 184) | DFMO/Sulindac (N = 191 ) | Placebo (N = 129) | DFMO/Sulindac (N = 138 ) |
| Characteristic | | | | |
| Age –yr | | | | |
| Median | 60 | 60 | 61 | 60 |
| Mean ± STD | 61± 8.2 | 60 ± 8.6 | 61± 7.9 | 60± 8.5 |
| Range | 42 - 78 | 41 - 79 | 42 - 78 | 41 - 78 |
| Male sex – no. (%) | 138 (75%) | 147 (77%) | 94 (73%) | 108 (78%) |
| Race or ethnic group – no. (%) | | | | |
| White | 158 (86%) | 155 (81%) | 110 (85%) | 115 (83%) |
| Black | 6 (3%) | 10 (5%) | 5 (4%) | 3 (2%) |
| Hispanic | 12 (7%) | 14 (7%) | 7 (5%) | 11 (8%) |
| Asian or Pacific Islander | 4 (2%) | 9 (5%) | 4 (3%) | 7 (5%) |
| Other | 4 (2%) | 3 (2%) | 3 (2%) | 2 (1%) |
| Body-mass index | | | | |
| Men (Mean ± STD) | 28.4 ± 4.5 | 29.2 ± 5.5 | 28.4 ± 4.37 | 29.3 ± 4.49 |
| Women (Mean ± STD) | 29.4 ± 7.5 | 27.7 ± 5.8 | 30.5 ± 8.0 | 26.6 ± 6.13 |
| Number of reported polyps (Mean ± STD) [1] | 2.51 ± 2.34 | 2.49 ± 2.15 | 2.45 ± 2.03 | 2.39 ± 2.06 |
| Largest adenoma ≥ 1 cm – no. (%)[2] | 40 (22%) | 38 (20%) | 28 (22%) | 27 (20%) |
| Use of low-dose aspirin – no. (%) | 69 (38%) | 77 (40%) | 50 (39%) | 53 (38%) |
| History of cardiovascular disease – no. (%)[3] | 67/155 (43%) | 73/158 (46%) | 54/110 (49%) | 51/114 (45%) |
| History of high blood pressure or hypertension – no. (%)[3] | 47/155 (30%) | 48/158 (30%) | 39/110 (35%) | 32/114 (28%) |
| History of diabetes – no. (%)[3] | 21/151 (14%) | 25/152 (16%) | 12/108 (11%) | 8/111 (7%) |
| Current or prior cigarette smoker – no. (%)[3, 4] | 41/99 (41%) | 42/100 (42%) | 20/67 (30%) | 23/67 (34%) |

All participants had a history of ≥1 resected adenoma ≥ 3mm, with the population as a whole stratified by ASA usage and study site. (It was hypothesised that aspirin use may affect response to DFMO/Sulindac.)

Treatment of polyps was categorised by: 1) endoscopic removal of polyps accounted for 94% of treatment received; 2) surgical removal accounted for the remaining 6%.

Participants could have a prior history of ≤ 10 days/month NSAID use and those who were taking baby aspirin (81 mg daily or 325 mg twice a week for CV prophylaxis) were eligible for study entry and could continue their use of ASA.

Discontinuation of study medication: Of the 375 subjects randomised to the Phase II and III cohorts, 119 subjects (32%) discontinued taking the study medication after having remained on study for an average of 399 days. Of these participants, 59 had been randomised to treatment 1 and 60 had been randomised to treatment 2.

Numbers analysed

- Phase IIB Planned 250 total participants to be enrolled with 125 randomized to each arm;
- Phase III Planned 150 total participants to be enrolled with 124 total participants to be randomized.
- Phase IIB and III participants were analyzed as a single cohort, with 502 total participants enrolled and 375 randomized (Phase IIB: 324 enrolled, 246 randomized; Phase III: 178 enrolled, 129 randomized)

| | Enrolled | Randomized | Active Drug | Placebo |
|---|---|---|---|---|
| DFMO IIB | 324 | 246 | 128 | 118 |
| DFMO III | 178 | 129 | 63 | 66 |

For the colon adenoma efficacy analysis, 267 participants with available data were included. Only participants who did not have an off-treatment colonoscopy exam were excluded. Sixteen of 267 participants had discontinued the study prior to 36 months. On average, 76% of these 267 participants had a follow-up colonoscopy during the specified interval of 33 to 39 months. Early examinations were given to 49 of 267 participants (18%), although it should be noted that this percentage was due to early closure of the Phase III study (due to fulfilment of the study's objectives) as recommended by the DSMB. Examinations were given after 39 months to 14 individuals (5%). The average duration of follow-up was 34.6 ± 5.29 months.

Outcomes and estimation

The primary outcome was recurrent adenoma. Table 37 summarises information about the number of adenomas detected in 267 participants. Based on log-binomial regression with adjustment for covariates, statistical estimates of risk ratios and p-values are given.

At least one adenoma (tubular, tubulovillous, villous, cancer in situ, polypoid well differentiated adenocarcinoma, adenocarcinoma, hyperplastic polyp with focal adenomatous change, mild dysplasia) was detected in 71 participants.. Advanced adenomas were identified by considering size or tissue type. No cancers were detected in the DFMO/Sulindac treatment group. Cancers were detected in 3 participants (2%) in the placebo group.

**Table 37: Risk of adenomas**

| | Total (N=267) | | Follow-up colonoscopy completed 33 mo. to 39 mo. after beginning treatment (N = 204) | |
|---|---|---|---|---|
| **Variable** | Placebo (N = 129) | DFMO/Sulindac (N = 138) | Placebo (N = 97) | DFMO/Sulindac (N =107) |
| **Detection of any adenoma** | | | | |
| Cumulative incidence of adenomas detected at end of the treatment (%) | 55 (43%) | 17 (12%) | 42 (43%) | 12 (11%) |
| Risk ratio[1] (95% CI) | - | 0.29 (0.18, 0.48) | - | 0.26 (0.15, 0.47) |
| P value | - | < 0.0001 | - | < 0.0001 |
| **Detection of advanced adenomas** | | | | |
| Cumulative incidence of advanced adenomas detected at end of the treatment (%) | 12 (9%) | 1 (0.7%) | 10 (10%) | 1 (1%) |
| Risk ratio[2] (95% CI) | - | 0.08 (0.01, 0.59) | - | 0.09 (0.01, 0.70) |
| P value | - | 0.0005 | - | 0.0016 |
| **Detection of advance adenomas with size ≥ 1 cm** | | | | |
| Cumulative incidence of advanced adenomas with size ≥ 1 cm detected at end of the treatment (%) | 10 (8%) | 1 (0.7%) | 8 (8%) | 1 (1%) |
| Risk ratio[2] (95% CI) | - | 0.09 (0.01, 0.72) | - | 0.11 (0.01, 0.89) |
| P value | - | 0.002 | - | 0.007 |
| **Detection of multiple adenomas ( > 1)** | | | | |
| Participants with > 1 adenoma, incidence (%) | 21 (16%) | 1 (0.7%) | 16 (16%) | 1 (1%) |
| Risk ratio[3] (95% CI) | - | 0.04 (0.006, 0.31) | - | 0.05 (0.007, 0.38) |
| P value | - | 0.0018 | - | < 0.0001 |

[1] Relative risk estimation by log-binomial regression with adjustment for pre-study aspirin use (yes/no), gender, ethnicity (white/non-white), and age (continuous). The likelihood ratio test *p* values adjusted for covariates were reported.
[2] Relative risk estimation by log-binomial regression without adjustment for covariates, due to insufficient number of advanced adenomas in the DFMO plus Sulindac group. The likelihood ratio test *p* values adjusted for covariates were reported.
[3] Relative risk estimation by log-binomial regression with adjustment for pre-study aspirin use (yes/no), ethnicity (white/non-white), and age (continuous). The likelihood ratio test *p* values adjusted for covariates were reported.

**Table 38: Number of adenomas detected at follow-up colonoscopy (N=267)**

| | DFMO/Sulindac (N=138) | | Placebo (N=129) | | |
|---|---|---|---|---|---|
| Follow-up examinations | Pre-randomization aspirin use > 81 mg per day (N=53) | Pre-randomization aspirin use ≤ 81 mg per day (N=85) | Pre-randomization aspirin use > 81 mg per day (N=50) | Pre-randomization aspirin use ≤ 81 mg per day (N=79) | Total (N=267) |
| N = adenomas[1] | Patients N(%) | Patients N(%) | Patients N(%) | Patients N(%) | Patients N(%) |
| 0 | 45 (85%)[2] | 76 (89%)[3] | 22 (44%)[4] | 52 (66%)[5] | 195 (73%)[6] |
| 1 | 8 (15%) | 8 (9%) | 15 (30%) | 19 (24%) | 50 (19%) |
| 2 | 0 | 1 (1%) | 6 (12%) | 5 (6%) | 12 (4%) |
| ≥ 3 | 0 | 0 | 7 (14%) | 3 (4%) | 10 (4%) |
| Mean of no. of adenomas ± SD | 0.15 ± 0.36 | 0.12 ± 0.36 | 1.04 ± 1.26 | 0.52 ± 0.93 | 0.42 ± 0.86 |
| Range of no. of adenomas | 0 - 1 | 0 - 2 | 0 - 5 | 0 - 5 | 0 - 5 |

[1]Number of adenomas is defined as the cumulative counts of adenomas from all follow-up colonoscopies
[2]Denominator=53; [3]Denominator=85; [4]Denominator=50; [5]Denominator=79; [6]Denominator=267

**CAT-001: Additional Analyses of the Data from the PSCA Study Evaluating Treatment with a Combination of Eflornithine and Sulindac**

Additional analysis was performed by CPP from 01 March 2020 to 01 April 2020.

As the original study involved one continuous study population with all collected data analysed at completion of the study, CAT-001 treats these two subject cohorts as components of a single Phase 3 study.

In these additional analyses, efficacy data from the original study population were analysed using the following analysis populations:

**Intent-to-Treat (ITT) Set:** The ITT analysis dataset included all subjects randomised. The original study randomised a total of 375 subjects, however 4 subjects (3 from Cohort 1 and 1 from Cohort 2) did not receive any randomised study drug. Those 4 subjects were analysed in their randomised treatment group. The ITT analysis is used to compare the initially randomised subjects regardless of what treatment subjects received.

**Treatment Completer Analysis (TCA) Set:** The planned treatment duration was 36 months. The TCA dataset set included all subjects who were on the treatment for ≥ 33 months (N = 222). In 2007, the Data and Safety Monitoring Committee recommended stopping the study early as the trial had met its primary efficacy goal but was judged to be too small to generate additional insights regarding possible treatment adverse events; historically at that time, this included the risk of NSAID induced Major Adverse Cardiac Events (MACE). This early stoppage of the trial resulted in the main difference between the TCA and PP data sets.

**Per Protocol (PP) Analysis Set:** The PP analysis set included all subjects who completed the study and who had ≥ 1 colonoscopy after treatment initiation (N = 230). The status of 'completed study' were defined based on the disposition page of the CRF. This group assesses the difference in outcome improvements in a subset of subjects who tolerated and adhered to the protocol. This analysis set addresses the efficacy hypotheses about the causal effects of the initially randomised drug.

**Modified Intent-to-Treat (mITT) Set:** The mITT analysis dataset set includes all subjects

who had at least 1 dose of study drug and who had ≥ 1 post treatment colonoscopy (N = 267).

There is no missing outcome data due to the definition and the exposure to the randomised treatment varies. This variation was addressed using the patient-year concept in the additional analysis of the incidence of advanced adenomas with size ≥ 1.

Treatment effect on the risk of adenomas was evaluated via a log-binomial regression method. A stepwise approach was used to evaluate treatment effect with and without covariates using four models.

**Model 1:** Simple model that includes only treatment effect. The risk ratio from this model is not adjusted by any covariates.

**Model 2:** Includes main effect of treatment and randomisation strata (pre-study use of low-dose aspirin (Y vs N)). This model will assess if this covariate will or will not have any effect on the treatment response. The risk ratio from this model is adjusted for the effect of pre-study use of low-dose aspirin.

**Model 3:** Includes the main effect of treatment, use of low-dose aspirin (Y vs N) prior to study, and subject cohort (Phase 2B vs Phase 3) to evaluate whether or not the study cohort had any impact on the treatment response in this study. The risk ratio from this model is adjusted for the effects of pre-study use of low-dose aspirin and study cohort.

**Model 4:** Includes the main effect of treatment and covariates of baseline factors, including pre-study use of low-dose aspirin (Y vs N), sex (M vs F), race group (white vs non-white), and age at baseline in years. The risk ratio from this model is adjusted for the effects of pre-study use of low-dose aspirin, race, sex and age at the baseline.

Missing Data

A total of 267 subjects had post-treatment colonoscopies, leaving 108 ITT (108/375 = 28.8%; 55 (29.9%) subjects in the combination treatment group and 53 (27.7%) in the placebo group with missing efficacy endpoint data.

**MNAR Scenario 1:** Missing data pattern is treatment group related. However, the subjects with missing data will follow the same pattern as those subjects in their corresponding randomised treatment group. Hence, only observations from their own treatment group will be used to derive the imputation model for the outcome. That is, the imputation will be performed separately within each treatment group.

**MNAR Scenario 2:** Subjects randomised to the combination treatment group will follow the same missing data pattern as the subjects randomised to the placebo group. Hence, only observations from placebo treatment group are used to derive the imputation model for the outcome.

**MNAR Scenario 3:** Subjects randomised to the placebo treatment group will follow the same missing data pattern as the subjects randomised to the combination group. Hence, only observations from the combination treatment group are used to derive the imputation model for the outcome.

**Table 39: Planned analyses of treatment effect on the risk for adenomas**

| Analysis No. | Analysis Population | Missing Mata Imputation Assumption | Classification |
|---|---|---|---|
| 1 | ITT | MCAR | Primary Analysis |
| 2 | ITT | MNAR – Scenario 1 | Sensitivity Analysis |
| 3 | ITT | MNAR – Scenario 2 | Sensitivity Analysis |
| 4 | ITT | MNAR – Scenario 3 | Sensitivity Analysis |
| 5 | TCA[1] | MCAR | Sensitivity Analysis |
| 6 | PP | NA (all subjects had colonoscopy per definition) | Sensitivity Analysis |
| 7 | mITT | NA (all subjects had colonoscopy per definition) | Sensitivity Analysis |

Abbreviations: NA = not applicable

[1] Per Listing 17.2.3, there are 2 subjects who completed the study treatment, but no colonoscopy was performed. Hence, missing data for the two subjects were imputed using the MCAR assumption. That is, the analysis datasets were taken directly from the imputed 20 complete datasets for the ITT analysis population for those subjects in this population.

CAT-001 ITT Results

**Table 40: PSCA study estimated relative risk of adenoma and 2-sided 95% CI using log-binominal regression models with and without adjustment of covariates - ITT population and other analyses population**

**Table 22 PSCA Study Estimated Relative Risk of Adenomas and 2-Sided 95% CI Using Log-Binominal Regression Models with and without Adjustment of Covariates – ITT Population and Other Analyses Populations**

| | Relative Risk of Adenomas (2-Sided 95% CI) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Missing Data Imputation Assumptions | | | | Analysis Population (Analysis Data)[2] | | |
| Model[1] | MCAR | MNAR – Scenario 1 | MNAR – Scenario 2 | MNAR – Scenario 3 | TCA (MCAR) | PP (Observed) | mITT (Observed) |
| Model 1 | 0.422 (0.273, 0.654) p = 0.0001 | 0.307 (0.186, 0.506) p < 0.0001 | 0.482 (0.324, 0.717) p = 0.0004 | 0.381 (0.232, 0.625) p = 0.0002 | 0.317 (0.187, 0.536) p < 0.0001 | 0.287 (0.171, 0.484) p < 0.0001 | 0.289 (0.177, 0.471) p < 0.0001 |
| Model 2 | 0.416 (0.270, 0.641) p < 0.0001 | 0.302 (0.184, 0.494) p < 0.0001 | 0.476 (0.323, 0.703) p = 0.0002 | 0.375 (0.229, 0.612) p = 0.0001 | 0.318 (0.189, 0.536) p < 0.0001 | 0.292 (0.174, 0.489) p < 0.0001 | 0.288 (0.178, 0.468) p < 0.0001 |
| Model 3 | 0.419 (0.272, 0.646) p < 0.0001 | 0.302 (0.184, 0.497) p < 0.0001 | 0.481 (0.325, 0.712) p = 0.0003 | 0.376 (0.230, 0.616) p = 0.0001 | 0.320 (0.190, 0.538) p < 0.0001 | 0.294 (0.175, 0.492) p < 0.0001 | 0.293 (0.180, 0.475) p < 0.0001 |
| Model 4 | 0.422 (0.274, 0.651) p = 0.0001 | 0.306 (0.185, 0.507) p < 0.0001 | 0.488 (0.332, 0.717) p = 0.0003 | 0.379 (0.232, 0.620) p = 0.0001 | 0.309 (0.183, 0.522) p < 0.0001 | 0.283 (0.169, 0.476) p < 0.0001 | 0.291 (0.179, 0.473) p < 0.0001 |

[1] Model 1 without any covariates; Model 2 included covariate ASA (Y vs N); Model 3 included covariate Cohort (2b vs 3); Model 4 included covariates ASA (Y vs N), sex (M vs F), race group (W vs NW), and baseline age (years, a continuous variable)

[2] TCA = Treatment Completer Analysis Population; PP = Per Protocol Population; mITT = Modified Intent-to-Treat Population

Abbreviations: ASA = pre-study aspirin use; F = Female; M = Male; MCAR = missing completely at random; MNAR = missing not at random; N = No; NW = non-White; W = White; Y = Yes.

Secondary Efficacy Endpoints

Treatment effect on the risk for any advanced adenomas and the risk for advanced adenoma size ≥ 1 cm was assessed using the same approach as the primary efficacy endpoint. The analyses focused on the ITT population and the mITT population. The ITT analysis included the imputed data produced with multiple imputations under the assumption of MCAR whereas the mITT analysis included all observed data.

**Table 41: Log-binominal regression analysis of risk for advanced adenomas - MCAR analysis using MI for missing data ITT analysis set**

| | Statistics [1] | Eflornithine + Sulindac (N = 191) | Placebo (N = 184) |
|---|---|---|---|
| Before Imputation | Subjects without any colonoscopy [2] | 53 (27.7) | 55 (29.9) |
| | Subjects with ≥ 1 colonoscopy [2] | 138 (72.3) | 129 (70.1) |
| | Subjects with any advanced adenomas detected [3] | 2 / 138 (1.4) | 13 / 129 (10.1) |
| | | | |
| Post Imputation Model 1 Analysis | Parameter | Estimate (SE) in log scale | Wald's Chi-sq Test P-value |
| | Intercept | -2.390 (0.271) | < .0001 |
| | Treatment (A vs P) | -1.237 (0.652) | 0.0601 |
| | **Risk Ratio (A/P) Estimate (Linear Scale) [4]** | **0.290** | |
| | **95% Confidence Limits: Lower, Upper** | **0.080, 1.055** | |
| | | | |
| Post Imputation Model 2 Analysis | Parameter | Estimate (SE) in log scale | Wald's Chi-sq Test P-value |
| | Intercept | -2.806 (0.402) | < .0001 |
| | Treatment (A vs P) | -1.253 (0.650) | 0.0562 |
| | ASA (Y vs N) | 0.842 (0.504) | 0.0964 |
| | **Adjusted Risk Ratio (A/P) Estimate (Linear Scale) [4]** | **0.286** | |
| | **95% Confidence Limits: Lower, Upper** | **0.079, 1.034** | |
| | | | |
| Post Imputation Model 3 Analysis | Parameter | Estimate (SE) in log scale | Wald's Chi-sq Test P-value |
| | Intercept | -2.850 (0.486) | < .0001 |
| | Treatment (A vs P) | -1.254 (0.651) | 0.0564 |
| | ASA (Y vs N) | 0.844 (0.503) | 0.0947 |
| | Cohort (1 vs 2) | 0.060 (0.469) | 0.8975 |
| | **Adjusted Risk Ratio (A/P) Estimate (Linear Scale) [4]** | **0.285** | |
| | **95% Confidence Limits: Lower, Upper** | **0.079, 1.035** | |

[1] Abbreviations: Treatment: A = Active (Eflornithine + Sulindac), P = Placebo; ASA = pre-study of low dose aspirin use: Y = Yes, N = No; Sex: M = male, F = Female;

Race Group: W = White, NW = Non-White; SE = Standard error

[2] Percent was calculated based on total subjects in the treatment group specified in the header (N)

[3] Percent was calculated based on subjects with ≥ 1 colonoscopy.

[4] Risk ratio of having an event.

## 2.5.3. Discussion on clinical efficacy

The applicant initially sought a CMA for Flynpovi (Eflornithine 288.6 mg / Sulindac 75 mg), " to be used as long-term treatment in addition to standard of care" "to delay the need for major surgery or resection of advanced adenoma in the intact colon (no prior large bowel resection), rectum, or ileo-anal pouch in adult patients with familial adenomatous polyposis (FAP). Clinical data in support of this proposed indication comes from a single Phase III pivotal double-blind randomised study in patients with FAP, CPP-FAP 310. The applicant also considers as supportive, a Phase III double blind randomised placebo-controlled study in patients with prior history of sporadic colorectal adenoma, PSCA.

FAP is an orphan condition, for which Flynpovi has been granted orphan designation.

No dose response studies were conducted for the combination CPP-1X (eflornithine) + sulindac to inform the proposed dose, CPP-1X 750 mg and sulindac 150 mg. The applicant cites studies that were based on the assumption that reducing mucosal polyamine levels will be associated with reducing polyp formation in the colon. Due to the dated and academic nature of many of these studies and the lack of binding affinity data and accurate dosage information, they do not provide robust data on the optimal dose.

### *Design and conduct of clinical studies*

The applicant received Scientific Advice from CHMP on multiple occasions between 2011 and 2019.

CHMP strongly recommended the use of a primary endpoint that only includes time related events of surgical intervention, development of cancer or death. Inclusion of both time to surgical intervention as well as time-to-progression of Spigelman stage for duodenal polyposis were deemed acceptable. CHMP questioned the sulindac dose of 150mg, noting the majority of data had been collected with doses higher

than this, and also questioned the absence of a placebo comparator arm. CHMP did not consider that the proposed study, CPP FAP-310, discussed during Scientific Advice with the applicant would be sufficient to grant a full or a conditional marketing authorisation.

As background, the previously available therapy for FAP, Onsenal (Celecoxib) authorised under exceptional circumstances by CHMP in 2003 was voluntarily withdrawn by the MAH who were unable to provide confirmatory data regarding clinical benefit.

There is currently no approved pharmacotherapy for chemoprevention of FAP in the EU.

**Main Study CPP-FAP-310**

CPP-FAP 310, the single pivotal study, was a Phase 3 double blind, three arm randomised study which enrolled 171 adult patients with FAP with a confirmed APC mutation or clinical phenotype of FAP.

The applicant sought to demonstrate a benefit of combination CPP-1X + sulindac over two monotherapy arms, CPP-1X (eflornithine) and sulindac, neither of which have established benefit in the treatment of FAP.

Of note, the proposed co-formulated fixed-dose combination tablet of eflornithine and sulindac was not investigated in the pivotal trial CPP-FAP 310 and has not been studied in the proposed patient population with FAP.

The targeted population were adults with a diagnosis of phenotypic classic FAP with involvement of the duodenum and/or colon/rectum/pouch. Quite a broad patient population with FAP were eligible to be included; both younger patients pre-colectomy as well as patients who had already undergone surgery with subsequent IRA, IPAA or entire removal of lower GI anatomy with only a remaining ileostomy. The applicant devised a stratification into three projected event prognosis groups 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 had 2 or more of these disease sites, the most severe prognosis stratum was assigned for randomisation (e.g., worst > intermediate > best). Since a subject may have had more than 1 disease site involved, the study assessed time to any defined FAP-related event in the subject as a whole.

The primary endpoint which was the subject of Scientific Advice, was a novel composite endpoint of time to first FAP related event.

Disease progression was defined in the protocol "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."

In general, with investigator assessment, there is potential for a degree of subjectivity based on the individual investigator deciding when to classify endoscopic findings as meeting criteria for disease progression, with need for surgery or excisional intervention. Similarly, as the applicant has alluded to, the decision to perform surgery often takes into accounts different life events, individual patient situation etc.

Endoscopy images were captured on DVD or flash drive and sent to a central imaging lab for archiving. However, no independent review or audit has been performed on these endoscopy assessments. The applicant also provided a Calibration and Standardisation Report with the responses which showed variability within investigators determinations for a number of the endoscopy findings. This further raises a concern that there was no blinded independent review of investigator determinations at endoscopy. Further, there was a recommendation to investigators, that patients with <100 polyps or >1000 polyps should be excluded but it is unclear how this was communicated to investigators and how much additional

variability may have been introduced if some investigators applied this recommendation and others did not.

Follow-up endoscopies in this study were performed six monthly. It is essential that endoscopic surveillance would be continued as normally recommended during treatment with Flynpovi and this is emphasised in section 4.1 of the SmPC.

Follow-up of the subject for FAP-related surgeries continued, per protocol, until 30 days after the last dose of study drug, or for 6 months prior to March 2016. This duration of follow-up is considered inadequate for such a trial in which time to occurrence of subsequent FAP-related events is likely to be longer than 30 days. The risk of missing additional FAP events post study discontinuation is likely to be high.

The study duration was extended initially from 24 months to 36 months, and then to 48 months maximum duration of treatment. In May 2018, the applicant took the decision to complete all final subject visits by end of November 2018. The applicant states that this was due to many factors including significant slowing of number of FAP related-events and statistical projections with 49 subjects remaining on study.

It is notable that the protocol underwent 11 revisions from inception. Three of these were considered substantial (Versions 3.0, 4.0 and 5.0). Multiple additional concerns in relation to the statistical analysis plan and analyses performed were raised. These include concerns on control of Type I error, the assumption of non-informative censoring and the large number of post hoc analyses.

## *Efficacy data and additional analyses*

Between 2nd December 2013 and 12th November 2018, 169 subjects received at least one dose of double-blinded study drug.

The majority of patients were in the duodenal polyposis stratum n=100 (58.5%), followed by pre-colectomy stratum n=37 (21.6%) and lastly rectal/pouch polyposis stratum n=34 (19.9%). Only 37 patients still had intact colons at entry into study, therefore interpretation of results in this population is hampered by the low numbers in each of the three treatment arms. More than 75% of participants were post-colectomy with either IRA, IPAA or ileostomy. The targeted benefit of treatment could be considered different; between patients who are pre-colectomy in whom delay in a generally inevitable colon surgery might be achieved vs post-colectomy patients in whom potential further surgery could be delayed or even potentially avoided. For both groups, avoidance of progression to colorectal cancer or death will, of course, also be considered a benefit, but in general, this is already achieved with current standard of care, which includes regular surveillance endoscopies with endoscopic intervention as required.

Therefore, the potential benefit of treatment with CPP-IX + sulindac and where a potential unmet need remains for patients, could be considered as the following:

1. Delaying colectomy in patient with intact colon

2. Delaying or potentially avoiding the need for additional rectal surgery/pouch surgery in patient with IRA/IPAA respectively.

3. Delaying or avoiding any potential need for ileostomy

4. Delaying progression of duodenal polyps in patient with duodenal disease

5. Delaying need for duodenal surgical intervention

6. Avoiding duodenal cancer

(Delaying time to next endoscopic surveillance which might also represent a benefit for patients was not investigated and thus it is imperative that no change to standard of care endoscopic surveillance should be considered whilst on Flynpovi).

The novel composite primary endpoint devised by the applicant sought to incorporate the above potential events within it; Time to First FAP-Related Event.

The study failed to meet its primary endpoint, in demonstrating a prolongation of time to first FAP-related event from time of randomisation, for the combination arm compared to either monotherapy arm.

The hazard ratio for the combination (CPP1X + sulindac) vs. sulindac was 0.71 (95% CI: 0.4, 1.3) with a nonsignificant p-value of 0.2898. The hazard ratio for the combination vs. CPP-1X was 0.66 (95% CI: 0.4, 1.2) with a nonsignificant p-value of 0.2001.

The percentage of subjects with a FAP-related event was: Combination treatment group 32.1% (18 of 56), Sulindac treatment group 37.9% (22 of 58), CPP-IX treatment group 40.4% (23 of 57). The applicant had estimated a higher number of FAP-related events would occur in both monotherapy arms. The absence of a placebo arm makes interpretation of the results challenging.

Thus, no benefit has been demonstrated for improving patient's time to first FAP-related event with the combination therapy as had been pre-specified by the applicant.

Additionally, no statistically significant difference between the combination treatment group and either single-agent treatment group for time from the date of randomisation to the date of the first occurrence of any FAP-related event was observed in the pre-specified analyses by disease stratum group (pre-colectomy, duodenal polyposis, and rectal/pouch polyposis)

At time of the first Scientific Advice in 2011, the CHMP had advised that the proposed evidence would unlikely be sufficient for either a full or conditional marketing approval. Again, in July 2011, the CHMP noted that the type of MA would depend on results obtained from this pivotal trial and that superior efficacy of the combination therapy would need to be clearly demonstrated. In the 'Points to Consider document on Applications with 1. Meta-analyses and 2. One Pivotal study' CPMP/EWP/2330/99 it is explicitly stated that minimum requirement is generally one controlled study with statistically compelling and clinically relevant results. However, the applicant has failed to meet the primary endpoint and neither clinical benefit nor relevance of the combination CPP-1X + sulindac in patients with FAP has been demonstrated.

Following the lack of demonstrated efficacy for the primary endpoint, the applicant included a number of post-hoc exploratory analyses forming new combinations of disease site subgroups and subcategories of FAP-related events. The applicant proposed to retrospectively revise the original primary endpoint to remove two components: excisional intervention of a polyp ≥10mm in size or with HGD, and Spigelman Stage (SS) progression. It is not agreed that SS progression is not clinically relevant and whilst some limitations are acknowledged, currently it is the only clinical tool available for follow-up of non-ampullary duodenal disease in patients with FAP and is referenced in current clinical guidelines British Society of Gastroenterology 2020 and American College of Gastroenterologists 2015.

Despite some trends for improvement in CPP-1X + sulindac versus monotherapy arms in time to first occurrence of FAP related LGI events in subjects with LGI anatomy, excluding patients with ileostomy, censoring events of excision of ≥10mm polyps alone, censoring SS progression alone and censoring both excision of ≥10mm polyps and SS progression, none of these analyses are considered robust as they were all post-hoc exploratory analyses generated post un-blinding of the data. Such results should be confirmed prospectively in order to support any potential efficacy claims from combination CPP-1X + sulindac in patients with FAP.

As a general remark on the design and conduct of the clinical study CPP FAP-310, it can be concluded that the study appears to be closer to a Phase II exploratory trial that would assess the appropriateness of the definition of the primary endpoint, the extent of the clinical benefit and the relevant target population. It cannot be considered a pivotal study. Clinical development appears to be incomplete and the request of a marketing authorisation premature. This was communicated to the applicant during the most recent Scientific Advice in 2019.

The applicant's originally planned hypothesis that CPP-1X + sulindac would address an unmet need for patients with FAP along the spectrum of FAP with colonic, rectal and duodenal disease has subsequently been modified, post results, to remove claims for any benefit in duodenal disease.

The revised main secondary endpoint was a new outcome measure which lacks validation, UGIOI and LGIOI. The nature of this outcome measure appears very subjective and at risk of significant variation between individual investigators.

Measurement of urinary polyamine levels was initially the main secondary endpoint of the study but was subsequently demoted. The applicant considers this endpoint exploratory only. No relevant information can be obtained from the urinary polyamine analysis in this study.

The applicant has included a number of measures of HR QOL. However, results did not show any meaningful differences between the three arms.

*Supportive studies*

The supportive study PSCA, as well as additional regulatory analysis CAT-001, are considered to provide limited support to establish the efficacy of Flynpovi.

Differences in target population, older age of PSCA participants, differences in eflornithine dosing and introduction of a different formulation, comparison to placebo in PSCA vs active control arms in CPP-FAP 310 and a claim of efficacy based on a previously critiqued primary endpoint, are just some of the limitations in drawing any meaningful comparisons between both studies.

The applicant provided a rationale on the Pathobiological Relevance of Sporadic Polyposis to FAP and asserts that based on the commonality of APC mutations in FAP, sporadic adenomas and sporadic colorectal carcinoma, that FAP and sporadic adenomatous polyp formation can be viewed as two points on a continuum. Whilst the potential underlying pathological mechanism for polyp formation may be similar in both patients with FAP and those with sporadic adenoma formation, these are clearly two distinct conditions. Patients with FAP have a heterozygous germline pathogenic variant in APC that is confirmed by molecular genetic testing. However, inactivating mutations of the APC gene are found in only ~ 80% of human colon tumours overall. Additionally, ongoing research is needed to better understand modifiers of APC in colon cancer and differences in severity and phenotype of FAP, thus the applicant's claim that the FAP and sporadic colorectal polyps, are simply on a continuum could be considered oversimplification of a more complex process (Kwong LN, Dove WF, Adv Exp Med Biol 2009; Houlston, Crabtree, Phillips et al, Gut 2001). Differences are known to exist between 'normal' colonic mucosa and the mucosa of patients with FAP. As an example, distinct histologic features in FAP such as the presence of microadenomas, dysplastic or adenomatous epithelial cells in single crypts or even portions of single crypts on biopsy of normal appearing mucosa, have been reported (Bussey HJR, 1975), as well as increased frequency of budding of dysolastic epithelium from normal crypts in FAP biopsies (Roncunni L, 1991).

Any demonstration of efficacy of combination eflornithine + sulindac in patients with history of sporadic colon polyps cannot be simply extrapolated to patients with the orphan condition of FAP. The results of PSCA (and CAT-001) appear to provide evidence of the superiority of combining eflornithine + sulindac over placebo, in reducing occurrence of new polyps over a 3 year period, in patients with history of

sporadic colonic polyps, however the results cannot compensate for the failed pivotal study in patients with FAP.

During the procedure, the applicant has further revised the proposed indication for Flynpovi as follows:

"Flynpovi is indicated as an adjunct to standard of care endoscopic surveillance for delaying the need for major surgery or resection of advanced adenoma in adult patients with familial adenomatous polyposis (FAP)."

The pivotal study CPP-FAP 310 has not demonstrated a statistically significant effect on the pre-specified primary endpoint of time to first FAP-related event. It has not been demonstrated that Flynpovi offers benefit to patients 'as an adjunct to standard of care'. The single clinical study performed by the applicant appears to be closer to a Phase II exploratory trial and as cautioned during Scientific Advice, the request for MA is considered premature.

During an oral explanation in front of the CHMP, the applicant stated that:

- The lower GI subgroup is a well-defined entity and was based on the pharmacological /preclinical rationale and clinical justification from the prior sporadic adenoma prevention trial.
- The observed treatment effects are underpinned by the pathophysiology of FAP, and the mechanism of disease shared between sporadic colon carcinogenesis and FAP.
- Eflornithine/sulindac combination delays/prevents Lower GI surgeries, which provides clear benefit to patients.
- The safety profile is well-characterised, acceptable and manageable.
- Benefit was demonstrated compared to each active component of the combination, a higher barrier than a placebo comparator.
- Based on the strong biological plausibility for an enhanced effect of Flynpovi in Lower GI and independent external support "replicating" an effect in Lower GI polyposis prevention from the PSCA, the strength of evidence offsets the formal failure of the study.

No new information or data could be provided to overcome the failure of the single pivotal study. The justifications provided by the applicant did not resolve the concerns raised by the CHMP. Therefore, as this was not resolved the benefit is not considered established.

## *Additional efficacy data needed in the context of a conditional MA*

Flynpovi was granted Orphan designation in January 2013 in the following condition: Treatment of familial adenomatous polyposis. Thus, it falls under the scope of Article 2 of the Conditional Marketing Authorisation (CMA) Regulation (EC) No. 507/2006.

The applicant argues that each of the four requirements in the article 4 of the Conditional Marketing Authorisation (CMA) Regulation (EC) No. 507/2006 are fulfilled.

In the context of a conditional MA, the applicant proposed to conduct a follow-up study in adults and adolescents with FAP to demonstrate Flynpovi can effect a reduction in the need for and to delay the time for major surgeries or the development of pre-cancerous adenomas in the lower GI tract compared to sulindac alone. From the limited information provided on the proposed confirmatory study FAP-325, concerns are already evident with the primary objective, lack of a placebo arm, failure to justify doses, as well as the envisaged difficulty of enrolling patients with this rare disease, especially if Flynpovi were to receive a CMA. Furthermore, the rationale is still not considered substantiated at present to justify enrolling multiple additional patients into a clinical trial.

In view of the negative benefit-risk, no conclusion can be reached at this stage on Specific Obligations to collect additional efficacy data in the context of a conditional MA.

Based on the currently available data, the applicant's request for a CMA cannot be supported.

### 2.5.4. Conclusions on the clinical efficacy

The applicant is seeking a CMA for Flynpovi based on results of a single pivotal study which failed to meet its primary endpoint. During the procedure, the applicant has revised the indication for Flynpovi to only include patients with intact lower GI anatomy, based on results obtained from a number of post-hoc, exploratory analyses which can at best be considered hypothesis generating. The applicant is essentially seeking efficacy in a subpopulation "tailored" post-hoc, by pooling the predefined pre-colectomy and rectal/pouch polyposis strata. The applicant has failed to present any biological rationale to support this seemingly data-driven new subgroup of patients with intact lower GI anatomy. Overall the presented data have not shown evidence for clinical benefit of Flynpovi in treating patients with FAP as an adjunct to standard of care.

The benefit of Flynpovi is currently not established and subsequently the product is not recommended for a conditional marketing authorisation.

## *2.6. Clinical safety*

***Patient exposure***

The safety results are obtained from 3 PK studies and 1 clinical study as listed below:

1. Single Dose Crossover Study in Healthy Patients (CPP-P9-658) – the PK pilot bioequivalence study.
2. Single Dose Parallel-Group Study in Healthy and Impaired Subjects (ELA P4-466) – the PK renal impairment study.
3. Single Dose Crossover Study in Healthy Subjects (CPP-P6-366) – the PK and food effect study.
4. Double-Blind Randomised Phase III Trial in Subjects with FAP (CPP FAP-310) – the clinical pivotal efficacy & safety study.

In addition, there are supportive data from an external pharmacoprevention of sporadic colorectal adenomas study (PSCA) with an updated analysis study of the data (CAT 001): *Difluoromethylornithine Plus Sulindac for the Prevention of Sporadic Colorectal Adenomas: A Randomized Placebo-Controlled, Double Blind Trial.*

Supportive external safety data from the above PSCA study were provided as published literature: Meyskens et al. 2008 *"Difluoromethylornithine Plus Sulindac for the Prevention of Sporadic Colorectal Adenomas: A Randomized Placebo-Controlled Double-Blind Trial",* McLaren et al. 2008 *"Longitudinal Assessment of Air Conduction Audiograms in a Phase III Clinical Trial of Difluoromethylornithine and Sulindac for Prevention of Sporadic Colorectal Adenomas"* and Zell et al. 2009 *"Risk of Cardiovascular Events in a Randomized Placebo-Controlled, Double-Blind Trial of Difluoromethylornithine Plus Sulindac for the Prevention of Sporadic Colorectal Adenomas".*

In total, 375 subjects were randomised to the investigational drug. 8.6% of the total randomised population was exposed to the investigational agent for < 6 months, 7.0% for 6 to 12 months, 5.8% for

12 to 18 months, 6.5% for 18 to 24 months, 9.7% for 24 to 30 months, and 22.4% for 30 to 36 months. Overall, 40% of the total population randomised was exposed to treatment for ≥ 36 months.

The focus of the clinical safety assessment is the pivotal patient study CPP-FAP-310.

Data from a pooled safety analyses of the pivotal study 310 and the supportive PSCA study also contributed to support the safety of the medicinal product.

**Table 42: Total numbers of Subjects at Risk for Colorectal Cancer in the Pooled ISS treatment group – Study CPP FAP-310 and the PSCA study**

| | Total Unique ISS Subjects | ES-Combo Overall (N = 244) | ES-Combo 750/150 mg (N = 56) | ES-Combo 500/150 mg (N = 188) | Eflornithine 750 mg (N = 56) | Sulindac 150 mg (N = 57) | Placebo (N = 183) |
|---|---|---|---|---|---|---|---|
| Study 310 | 169[a] | 56 | 56 | 0 | 56 | 57 | 0 |
| PSCA Study | 371[b] | 188 | 0 | 188 | 0 | 0 | 183 |
| Total | 540 | 244 | 56 | 188 | 56 | 57 | 183 |

[a] Excluded 2 randomized but not treated ITT subjects

[b] Excluded 4 randomized but not treated ITT subjects

**Table 43: Total drug exposure summary in subjects at risk for colorectal cancer – study CPP FAP-310 and the PSCA study**

| | ES-Combo Overall (N=244) | ES-Combo 750/150 mg (N=56) | ES-Combo 500/150 mg (N=188) | Eflornithine 750 mg (N=56) | Sulindac 150 mg (N=57) | Placebo (N=183) |
|---|---|---|---|---|---|---|
| Treatment Duration (months) | | | | | | |
| N | 243 | 55 | 188 | 54 | 57 | 183 |
| Mean (SD) | 27.57 (12.521) | 23.77 (13.958) | 28.69 (11.880) | 20.51 (12.239) | 21.27 (13.440) | 27.95 (11.796) |
| Median | 35.22 | 24.28 | 35.60 | 21.86 | 18.53 | 35.32 |
| Min, Max | 0.5, 48.5 | 0.5, 48.5 | 0.6, 43.7 | 1.1, 48.7 | 0.0, 47.9 | 1.2, 42.9 |
| | | | | | | |
| Distribution, n (%) | | | | | | |
| ≤6 Months | 23 (9.5) | 7 (12.7) | 16 (8.5) | 8 (14.8) | 8 (14.0) | 16 (8.7) |
| >6 and ≤12 Months | 21 (8.6) | 7 (12.7) | 14 (7.4) | 7 (13.0) | 11 (19.3) | 13 (7.1) |
| >12 and ≤24 Months | 33 (13.6) | 12 (21.8) | 21 (11.2) | 19 (35.2) | 13 (22.8) | 24 (13.1) |
| >24 and ≤36 Months | 84 (34.6) | 16 (29.1) | 68 (36.2) | 14 (25.9) | 14 (24.6) | 57 (31.1) |
| >36 and ≤48 Months | 81 (33.3) | 12 (21.8) | 69 (36.7) | 5 (9.3) | 11 (19.3) | 73 (39.9) |
| >48 Months | 1 (0.4) | 1 (1.8) | 0 | 1 (1.9) | 0 | 0 |
| | | | | | | |
| Cumulative Distribution, n (%) | | | | | | |
| Up to 6 Months | 243 (100.0) | 55 (100.0) | 188 (100.0) | 54 (100.0) | 57 (100.0) | 183 (100.0) |
| Up to 12 Months | 220 (90.5) | 48 (87.3) | 172 (91.5) | 46 (85.2) | 49 (86.0) | 167 (91.3) |
| Up to 24 Months | 199 (81.9) | 41 (74.5) | 158 (84.0) | 39 (72.2) | 38 (66.7) | 154 (84.2) |
| Up to 36 Months | 166 (68.3) | 29 (52.7) | 137 (72.9) | 20 (37.0) | 25 (43.9) | 130 (71.0) |
| Up to 48 Months | 82 (33.7) | 13 (23.6) | 69 (36.7) | 6 (11.1) | 11 (19.3) | 73 (39.9) |
| > 48 Months | 1 (0.4) | 1 (1.8) | 0 | 1 (1.9) | 0 | 0 |

Abbreviations: ES-combo = Eflornithine + Sulindac either co-formulated or co-administered; N or n = number; SD = standard deviation

Safety of the mono-components

**Table 44: Summary of Safety from clinical trials assessing sulindac alone**

| # Subjects | Sulindac Dose (daily oral) | Duration of Dosing | Toxicities | Ref. |
|---|---|---|---|---|
| 49,907 | 300-400 mg/day | 3-52 weeks | This report summarized 9 separate trials assessing side effects including gastrointestinal (10-21%), tinnitus (0-8%), headache (1-9%), skin rash (1-11%), and peripheral oedema (1-3%) depending on the trials cited. | (Coles et al. 1983) |
| 25,000 | 300-400 mg/day | 1-72 weeks | The incidence of adverse effects including abdominal pain (7.2%), nausea (6.5%), constipation (3.0%), dizziness (2.7%), drowsiness (2.1%), headache (1.7%), and diarrhoea (1.5%) were observed. Sulindac was generally been well tolerated and only occasionally (about 3 to 7%) patients withdrew because of side effects. | (Brogden et al. 1978) |
| 63 | 300 mg/day | 2 months | The incidence of adverse events, including symptoms such as abdominal pain, heartburn, diarrhoea, and exanthema, and abnormal laboratory test results such as a transient elevation of ALT or creatinine was less than 4% and all were grade 1. No differences between treatment groups were observed. Additionally, no cardiovascular events were observed during the 2 months of treatment. Average compliance with medication was > 91% in all treatment groups. | (Takayama et al. 2011) |
| 41 | 150 mg/day or 300 mg/day | 48 months | After 4 years of treatment, the mean rate of compliance was 87% in the sulindac group. Treatment with sulindac for a four-year period as well tolerated. Few adverse events were reported, and 93 percent of these were minimal (grade 1) or mild (grade 2). In this study only 1 subject withdrew because of possible drug-induced persistent neutropenia. The incidence of any adverse event did not differ significantly between the sulindac group and the placebo group. | (Giardiello et al. 2002) |
| 22 | 300 mg/day | 9 months | No adverse events were attributed to sulindac treatment in this study even with an overall compliance rate of 85%. | (Giardiello et al. 1993) |
| 12 | 158 mg/day | 14-98 months | Very few adverse events were noted in the study with the most common being rectal mucosal erosion occurring in 50% of the patients at a mean interval of 25.3 months. These mucosal erosions occurred at the IRA site. Perturbations in laboratory studies were not noted. | (Cruz-Correa et al. 2002) |

**Table 45: Summary of safety from clinical trials assessing eflornithine alone or in combination with other agents**

| # Subjects (randomized) | Eflornithine dose (daily oral) | Duration of Dosing | Toxicities | Ref. |
|---|---|---|---|---|
| 454 | 1 gm/day | 1 year | Low-6.6 (eflornithine) versus 5.7 (placebo) % serious adverse event | (Messing et al. 2006) |
| 375 | 500 mg/day | 3 years | Analysis of ototoxicity in this trial found no significant difference in the proportion of patients in the treatment arm who experienced clinically significant hearing loss compared with the placebo group and a <2 dB difference in mean pure tone threshold for patients on treatment compared with those on placebo. A non-statistically-significant increase in cardiovascular events at the end of treatment in this trial was similar in number to an excess of patients with cardiovascular risk factors at baseline in the treatment compared to placebo arms of this trial. | (Meyskens et al. 2008), (McLaren et al. 2008), and (Zell et al. 2009). |
| 291 | 500 mg/m$^2$/day | 4-5 years | Evidence of mild ototoxicity | (Bailey et al. 2010) |
| 119 | 0.5 g/m$^2$/day | 6-8 months | There were no differences in the incidence or intensity of adverse events in the placebo versus eflornithine groups. GI toxicity (nausea, dyspepsia, flatulence, and diarrhoea) occurred in 34% of the subjects randomized to the eflornithine group and in 32% of subjects randomized to the placebo group. There was no difference between the eflornithine (27%) and placebo (25%) groups for reported tinnitus. | (Fabian et al. 2002) |
| 118 | 0.075 to 0.4 g/m$^2$/day | 1 year | The most frequent AE was hearing loss; the most serious AEs (leading to discontinuation of subjects from the study) were grade 2 and 3 dizziness/vertigo, hearing loss, and speech difficulty | (Meyskens et al. 1998). |
| 111 | 500 mg/m$^2$/day | 6 months | No differences in toxicities, including autotoxicities, were observed between treatment arms in this study. | (Lynch et al. 2016) |
| 111 | 0.1 to 3.0 g/m$^2$/day | 4 weeks | The most frequent AEs were mild, transient epigastric pain, diarrhoea, nausea; the most serious AE was one case of abdominal pain (due to gallstones). Also, two subjects were discontinued from the study due to myocardial infarction and atrial fibrillation, both unrelated to drug. None of the 30 subjects receiving either 0.25 or 0.5 g/m$^2$ experienced clinical ototoxicity in this trial. | (Meyskens et al. 1994) |

| # Subjects (randomized) | Eflornithine dose (daily oral) | Duration of Dosing | Toxicities | Ref. |
|---|---|---|---|---|
| 98 | 3.6 g/m²/day | 1 year | Grade 3 ototoxicity was reported in 12 patients (14%) and tinnitus (grade 2) was reported for 2 patients (2%). Other toxicities included diarrhoea (13% at grade 1, 16% at grade 2, 3% at grade 3, and 1% at grade 4) and leukopenia (18% at grade 1, 16% at grade 2, and 2% at grade 3). | (Levin et al. 1992) |
| 81 | 500 mg/day | 1 year | No statistically and clinically significant toxicities | (Simoneau et al. 2008) |
| 79 | 0.125 to 1.0 g/day | 1 year | Grade 1 diarrhoea and nausea. No substantial drug-related toxicities were observed at any dose; thus, doses up to 1 g qd were well tolerated for up to one year. | (Loprinzi et al. 1996) |
| 58 | 2 to 12 g/m²/day | 50 weeks | Cumulative eflornithine doses showed a consistent and statistically significant positive relationship to ototoxicity. Patients with normal hearing demonstrated more eflornithine-related hearing loss compared with patients with abnormal hearing. Significant ototoxicity was reported in 75% of the patients who received cumulative eflornithine doses above 250 g/m² (~6180 mg/kg or 432,600 mg). In contrast, minimal ototoxicity was reported for patients who received a cumulative eflornithine dose below 150 g/m² (~3700 mg/kg or 259,000 mg). | (Croghan, Aickin, and Meyskens 1991) |
| 45 | 500 mg/m²/day | 1 year | Grade 1 and 2 tinnitus, hearing loss, anaemia, diarrhoea, abdominal pain, and skin rash. The most serious AEs were grade 2 tinnitus (7 cases), diarrhoea (1), and pain (1). Three subjects experienced clinical hearing loss attributable to drug treatment; all cases of hearing loss were reversed after 3 to 12 months. | (Love et al. 1998) and (Pasic, Heisey, and Love 1997) |
| 36 | 0.125-0.75 g/m² qid and 0.5-1.0 g/m² qd | 6 months | The most frequent (and most serious) AEs were grade 3 hearing loss; other frequent AEs were grade 1 diarrhoea, nausea, and flatulence. TPA-induced ODC activity was reduced by 34% and 64% in the samples from the 0.5 g/m² qd and 0.125 g/m² qid cohort. A single daily dose of 0.5 g/m² (~12.3 mg/kg or 861 mg/day for 70 kg adult) was selected for a subsequent study using 5-12 months of treatment. | (Love et al. 1993) |
| 27 | 0.2 g/m²/day to 6.4 g/m²/day | 6 months | The most frequent (and most serious) AEs were grade 3 hearing loss. Based on these results it was suggested that the dose for chemoprevention trials should not exceed 1.6 g/m²/day (39.5 mg/kg/day or 2765 mg/day for 70 kg adult). | (Creaven, Pendyala, and Petrelli 1993; Pendyala, Creaven, and Porter 1993) |
| 10 | 500 mg/m²/day | 6 months | 1 pt with subclinical ototoxicity | (Sinicrope et al. 2011) |
| 10 | 0.5 to 2.0 g/m²/day IV | 32 weeks | There were no hepatic toxicities or cholecystitis reported in this study. Mild pruritus was observed in three patients. The dose-limiting adverse effect was ototoxicity, encountered in all patients who received a daily dose of eflornithine ³1.0 mg/m² (~24.7 mg/kg/day or 1729 mg/day for 70 kg adult). | (Lipton et al. 1989) |

## *Adverse events*

### CPP-FAP-310

**Table 46: Summary of adverse events (Safety population)**

| | ES-Co-Administered N=56 | Sulindac N=57 | Eflornithine N=56 |
|---|---|---|---|
| Number of TEAEs, n | 417 | 398 | 419 |
| Patients with any TEAE, n (%) | 52 (92.9) | 50 (87.7) | 49 (87.5) |
| Number of Treatment-Related AEs, n | 133 | 173 | 171 |
| Number of Patients with a Treatment-Related AEs, n (%) | 38 (67.9) | 42 (73.7) | 31 (55.4) |
| Number of TEAE of Grade 3 or Higher, n | 21 | 21 | 19 |
| Patients with a TEAE of Grade 3 or Higher, n (%) | 12 (21.4) | 12 (21.1) | 17 (30.4) |
| Number of Serious AEs, n | 19 | 13 | 16 |
| Patients with a Serious AEs, n (%) | 11 (19.6) | 11 (19.3) | 14 (25.0) |
| Number of Treatment-Related Serious AEs, n | 3 | 4 | 1 |
| Patients with a Treatment-Related Serious AEs, n (%) | 3 (5.4) | 4 (7.0) | 1 (1.8) |
| Number of AEs Leading to Discontinuation of Study Drug, n | 13 | 7 | 6 |
| Patients with an AE Leading to Discontinuation of Study Drug, n (%) | 9 (16.1) | 6 (10.5) | 5 (8.9) |
| Patients with an AE Leading to Death, n (%) | 0 | 0 | 0 |

Source: Study CPP FAP-310, Table 14.3.1.1

Common Adverse Events

**Table 47: Summary of TEAEs Reported by ≥ 10.0% of Subjects in any treatment group (safety population)**

| System Organ Class<br>Preferred Term | Combination N=56 | Sulindac N=57 | CPP-1X N=56 |
|---|---|---|---|
| | n (%) of Subjects | | |
| Subjects with at least 1 TEAE | 52 (92.9) | 50 (87.7) | 49 (87.5) |
| Ear and labyrinth disorders | 6 (10.7) | 10 (17.5) | 6 (10.7) |
| Tinnitus | 2 (3.6) | 6 (10.5) | 1 (1.8) |
| Gastrointestinal disorders | 40 (71.4) | 35 (61.4) | 35 (62.5) |
| Nausea | 12 (21.4) | 12 (21.1) | 9 (16.1) |
| Vomiting | 6 (10.7) | 10 (17.5) | 7 (12.5) |
| Diarrhoea | 7 (12.5) | 6 (10.5) | 8 (14.3) |
| Abdominal pain | 8 (14.3) | 8 (14.0) | 4 (7.1) |
| Rectal haemorrhage | 7 (12.5) | 7 (12.3) | 4 (7.1) |
| Haematochezia | 6 (10.7) | 2 (3.5) | 6 (10.7) |
| Abdominal pain upper | 7 (12.5) | 1 (1.8) | 4 (7.1) |
| General disorders and administration site conditions | 17 (30.4) | 15 (26.3) | 15 (26.8) |
| Fatigue | 4 (7.1) | 8 (14.0) | 8 (14.3) |
| Infections and infestations | 30 (53.6) | 26 (45.6) | 27 (48.2) |
| Nasopharyngitis | 6 (10.7) | 4 (7.0) | 10 (17.9) |
| Upper respiratory tract infection | 8 (14.3) | 8 (14.0) | 2 (3.6) |
| Gastroenteritis | 7 (12.5) | 5 (8.8) | 4 (7.1) |
| Nervous system disorders | 13 (23.2) | 19 (33.3) | 17 (30.4) |
| Headache | 8 (14.3) | 11 (19.3) | 5 (8.9) |
| Dizziness | 4 (7.1) | 4 (7.0) | 6 (10.7) |
| Respiratory, thoracic and mediastinal disorders | 11 (19.6) | 12 (21.1) | 14 (25.0) |
| Cough | 3 (5.4) | 4 (7.0) | 6 (10.7) |
| Skin and subcutaneous tissue disorders | 20 (35.7) | 12 (21.1) | 14 (25.0) |
| Rash | 6 (10.7) | 2 (3.5) | 0 |

TEAE=treatment-emergent adverse event
Source: Table 14.3.1.2

**Table 48: Summary of TEAEs grade 3 or higher reported by >1 subject in any treatment group (safety population)**

| System Organ Class | Combination N=56 | Sulindac N=57 | CPP-1X N=56 |
|---|---|---|---|
| Preferred Term | n (%) of Subjects | | |
| Subjects with at least 1 TEAE grade 3 or higher | 12 (21.4) | 12 (21.1) | 17 (30.4) |
| Gastrointestinal disorders | 5 (8.9) | 5 (8.8) | 6 (10.7) |
| Ileus | 1 (1.8) | 0 | 2 (3.6) |
| Small intestinal obstruction | 2 (3.6) | 2 (3.5) | 1 (1.8) |
| Injury, poisoning, and procedural complications | 3 (5.4) | 4 (7.0) | 5 (8.9) |
| Ligament rupture | 2 (3.6) | 0 | 0 |
| Psychiatric disorders | 0 | 2 (3.5) | 0 |
| Depression | 0 | 2 (3.5) | 0 |

Treatment-Related Adverse Events

**Table 49: Summary of treatment related TEAEs reported by ≥5.0% of subjects in any treatment group (safety population)**

| System Organ Class<br>Preferred Term | ES-Co-Administered N=56 | Sulindac N=57 | Eflornithine N=56 |
|---|---|---|---|
| | n (%) of Subjects | | |
| Subjects with at least 1 treatment-related TEAEs[a] | 38 (67.9) | 42 (73.7) | 31 (55.4) |
| Ear and labyrinth disorders | 4 (7.1) | 6 (10.5) | 3 (5.4) |
| Tinnitus | 1 (1.8) | 5 (8.8) | 1 (1.8) |
| Gastrointestinal disorders | 28 (50.0) | 24 (42.1) | 26 (46.4) |
| Nausea | 9 (16.1) | 9 (15.8) | 8 (14.3) |
| Diarrhea | 4 (7.1) | 3 (5.3) | 5 (8.9) |
| Abdominal pain | 3 (5.4) | 4 (7.0) | 4 (7.1) |
| Rectal hemorrhage | 4 (7.1) | 4 (7.0) | 3 (5.4) |
| Vomiting | 2 (3.6) | 4 (7.0) | 5 (8.9) |
| Flatulence | 4 (7.1) | 3 (5.3) | 3 (5.4) |
| Dyspepsia | 2 (3.6) | 4 (7.0) | 3 (5.4) |
| Abdominal distension | 1 (1.8) | 3 (5.3) | 4 (7.1) |
| Abdominal pain upper | 5 (8.9) | 1 (1.8) | 2 (3.6) |
| Hematochezia | 2 (3.6) | 2 (3.5) | 4 (7.1) |
| Frequent bowel movements | 0 | 1 (1.8) | 3 (5.4) |
| Gastritis erosive | 3 (5.4) | 0 | 0 |
| General disorders and administration site conditions | 2 (3.6) | 6 (10.5) | 6 (10.7) |
| Fatigue | 1 (1.8) | 4 (7.0) | 3 (5.4) |
| Investigations | 7 (12.5) | 11 (19.3) | 6 (10.7) |
| Platelet count decreased | 0 | 3 (5.3) | 1 (1.8) |
| Metabolism and nutrition disorders | 3 (5.4) | 5 (8.8) | 5 (8.9) |
| Decreased appetite | 2 (3.6) | 4 (7.0) | 3 (5.4) |
| Nervous system disorders | 6 (10.7) | 14 (24.6) | 11 (19.6) |
| Headache | 3 (5.4) | 7 (12.3) | 5 (8.9) |
| Dizziness | 2 (3.6) | 2 (3.5) | 3 (5.4) |
| Psychiatric disorders | 1 (1.8) | 7 (12.3) | 4 (7.1) |
| Depression | 0 | 3 (5.3) | 1 (1.8) |
| Skin and subcutaneous tissue disorders | 13 (23.2) | 7 (12.3) | 7 (12.5) |
| Pruritus | 1 (1.8) | 4 (7.0) | 2 (3.6) |
| Rash | 6 (10.7) | 0 | 0 |
| Alopecia | 2 (3.6) | 3 (5.3) | 0 |

Source: Study CPP FAP-310. Table 14.3.1.4

Safety findings of the Integrated summary safety profile

**Table 50: TEAEs reported by ≥ 5.0% of subjects in any treatment group in subjects at risk for colorectal cancer by preferred term – study CPP FAP-310 and the PSCA study**

| Preferred Term | Total Events | ES-Combo Overall (N = 244) n (%) [Events] | Eflornithine 750 mg (N = 56) n (%) [Events] | Sulindac 150 mg (N = 57) n (%) [Events] | Placebo (N = 183) n (%) [Events] |
|---|---|---|---|---|---|
| Subjects with ≥ 1 Event | 3353 | 224 (91.8) [1525] | 49 (87.5) [419] | 50 (87.7) [398] | 155 (84.7) [1011] |
| Diarrhoea | 127 | 40 (16.4) [62] | 8 (14.3) [12] | 6 (10.5) [9] | 25 (13.7) [44] |
| Fatigue | 75 | 32 (13.1) [34] | 8 (14.3) [11] | 8 (14.0) [9] | 20 (10.9) [21] |
| Ototoxicity | 72 | 39 (16.0) [45] | 0 | 0 | 25 (13.7) [27] |
| Headache | 77 | 29 (11.9) [35] | 5 (8.9) [6] | 11 (19.3) [12] | 16 (8.7) [24] |
| Nausea | 86 | 25 (10.2) [33] | 9 (16.1) [14] | 12 (21.1) [21] | 12 (6.6) [18] |
| Nasopharyngitis | 71 | 25 (10.2) [37] | 10 (17.9) [14] | 4 (7.0) [4] | 13 (7.1) [16] |
| Back pain | 65 | 27 (11.1) [35] | 5 (8.9) [6] | 3 (5.3) [3] | 14 (7.7) [21] |
| Arthralgia | 66 | 20 (8.2) [29] | 5 (8.9) [8] | 3 (5.3) [3] | 20 (10.9) [26] |
| Abdominal pain | 58 | 20 (8.2) [31] | 4 (7.1) [4] | 8 (14.0) [10] | 11 (6.0) [13] |
| Vomiting | 63 | 17 (7.0) [20] | 7 (12.5) [10] | 10 (17.5) [23] | 7 (3.8) [10] |
| Tinnitus | 45 | 16 (6.6) [16] | 1 (1.8) [1] | 6 (10.5) [7] | 15 (8.2) [21] |
| Abdominal pain upper | 43 | 19 (7.8) [22] | 4 (7.1) [4] | 1 (1.8) [1] | 13 (7.1) [16] |
| Dyspepsia | 48 | 11 (4.5) [17] | 5 (8.9) [5] | 5 (8.8) [6] | 15 (8.2) [20] |
| Haemoglobin decreased | 43 | 18 (7.4) [22] | 1 (1.8) [1] | 0 | 16 (8.7) [20] |
| Upper respiratory tract infection | 48 | 15 (6.1) [22] | 2 (3.6) [3] | 8 (14.0) [10] | 10 (5.5) [13] |
| Rectal haemorrhage | 40 | 16 (6.6) [17] | 4 (7.1) [7] | 7 (12.3) [8] | 6 (3.3) [8] |
| Dizziness | 44 | 12 (4.9) [12] | 6 (10.7) [11] | 4 (7.0) [6] | 10 (5.5) [15] |
| Cough | 32 | 11 (4.5) [12] | 6 (10.7) [6] | 4 (7.0) [4] | 9 (4.9) [10] |
| Sinusitis | 32 | 16 (6.6) [17] | 5 (8.9) [5] | 2 (3.5) [3] | 7 (3.8) [7] |
| Hypertension | 31 | 14 (5.7) [17] | 2 (3.6) [2] | 0 | 10 (5.5) [12] |
| Influenza | 29 | 16 (6.6) [17] | 3 (5.4) [5] | 3 (5.3) [3] | 4 (2.2) [4] |
| Deafness | 28 | 13 (5.3) [15] | 0 | 0 | 12 (6.6) [13] |
| Haematochezia | 33 | 13 (5.3) [18] | 6 (10.7) [8] | 2 (3.5) [3] | 4 (2.2) [4] |
| Rash | 26 | 15 (6.1) [15] | 0 | 2 (3.5) [2] | 8 (4.4) [9] |
| Constipation | 34 | 11 (4.5) [15] | 5 (8.9) [7] | 2 (3.5) [3] | 6 (3.3) [9] |

| Preferred Term | Total Events | ES-Combo Overall (N = 244) n (%) [Events] | Eflornithine 750 mg (N = 56) n (%) [Events] | Sulindac 150 mg (N = 57) n (%) [Events] | Placebo (N = 183) n (%) [Events] |
|---|---|---|---|---|---|
| Gastroesophageal reflux disease | 33 | 13 (5.3) [15] | 2 (3.6) [3] | 2 (3.5) [2] | 7 (3.8) [13] |
| Pain in extremity | 29 | 13 (5.3) [15] | 2 (3.6) [2] | 1 (1.8) [1] | 8 (4.4) [11] |
| Urinary tract infection | 27 | 10 (4.1) [10] | 4 (7.1) [5] | 2 (3.5) [2] | 8 (4.4) [10] |
| Oropharyngeal pain | 25 | 8 (3.3) [9] | 5 (8.9) [5] | 1 (1.8) [1] | 9 (4.9) [10] |
| Decreased appetite | 25 | 8 (3.3) [9] | 4 (7.1) [4] | 5 (8.8) [5] | 4 (2.2) [7] |
| Paraesthesia | 25 | 11 (4.5) [13] | 0 | 1 (1.8) [1] | 9 (4.9) [11] |
| Weight decreased | 24 | 11 (4.5) [14] | 0 | 2 (3.5) [2] | 8 (4.4) [8] |
| Depression | 20 | 7 (2.9) [7] | 1 (1.8) [1] | 4 (7.0) [4] | 6 (3.3) [8] |
| Myalgia | 21 | 9 (3.7) [9] | 2 (3.6) [2] | 1 (1.8) [1] | 6 (3.3) [9] |
| Abdominal distension | 19 | 8 (3.3) [9] | 5 (8.9) [6] | 3 (5.3) [3] | 1 (0.5) [1] |
| Bronchitis | 18 | 8 (3.3) [8] | 1 (1.8) [1] | 3 (5.3) [3] | 5 (2.7) [6] |
| Flatulence | 17 | 7 (2.9) [7] | 3 (5.4) [3] | 3 (5.3) [3] | 3 (1.6) [4] |
| Gastroenteritis | 19 | 7 (2.9) [9] | 4 (7.1) [4] | 5 (8.8) [6] | 0 [0] |
| Anxiety | 17 | 4 (1.6) [4] | 1 (1.8) [1] | 4 (7.0) [6] | 5 (2.7) [6] |
| Musculoskeletal pain | 15 | 5 (2.0) [5] | 4 (7.1) [5] | 2 (3.5) [2] | 3 (1.6) [3] |
| Neck pain | 16 | 5 (2.0) [7] | 1 (1.8) [1] | 0 [0] | 8 (4.4) [8] |
| Influenza like illness | 18 | 5 (2.0) [7] | 5 (8.9) [7] | 3 (5.3) [4] | 0 [0] |
| Pruritus | 17 | 4 (1.6) [7] | 2 (3.6) [2] | 4 (7.0) [4] | 3 (1.6) [4] |
| Ear pain | 15 | 3 (1.2) [4] | 2 (3.6) [2] | 4 (7.0) [4] | 3 (1.6) [5] |
| Oedema peripheral | 15 | 5 (2.0) [6] | 3 (5.4) [4] | 1 (1.8) [1] | 3 (1.6) [4] |
| Procedural pain | 15 | 8 (3.3) [11] | 3 (5.4) [3] | 0 [0] | 1 (0.5) [1] |
| Insomnia | 15 | 4 (1.6) [8] | 2 (3.6) [2] | 4 (7.0) [4] | 1 (0.5) [1] |
| Contusion | 10 | 4 (1.6) [4] | 3 (5.4) [3] | 0 | 3 (1.6) [3] |
| Nasal congestion | 9 | 3 (1.2) [3] | 1 (1.8) [1] | 3 (5.3) [3] | 2 (1.1) [2] |
| Disturbance in attention | 7 | 1 (0.4) [1] | 0 [0] | 3 (5.3) [3] | 3 (1.6) [3] |
| Pouchitis | 7 | 3 (1.2) [3] | 2 (3.6) [2] | 2 (3.5) [2] | 0 [0] |
| Frequent bowel movements | 8 | 0 [0] | 3 (5.4) [3] | 1 (1.8) [1] | 2 (1.1) [4] |
| Seasonal allergy | 7 | 2 (0.8) [2] | 3 (5.4) [3] | 0 [0] | 1 (0.5) [2] |
| Small intestinal obstruction | 9 | 3 (1.2) [6] | 1 (1.8) [1] | 2 (3.5) [2] | 0 [0] |
| Weight increased | 6 | 2 (0.8) [2] | 3 (5.4) [3] | 1 (1.8) [1] | 0 [0] |
| Alopecia | 5 | 2 (0.8) [2] | 0 [0] | 3 (5.3) [3] | 0 [0] |
| Dry skin | 5 | 4 (1.6) [4] | 1 (1.8) [1] | 0 [0] | 0 [0] |
| Vitamin D deficiency | 5 | 0 [0] | 2 (3.6) [2] | 3 (5.3) [3] | 0 [0] |
| Eczema | 5 | 1 (0.4) [1] | 3 (5.4) [4] | 0 [0] | 0 [0] |
| Iron deficiency anaemia | 4 | 1 (0.4) [1] | 0 [0] | 3 (5.3) [3] | 0 [0] |
| Platelet count decreased | 5 | 0 [0] | 1 (1.8) [1] | 3 (5.3) [4] | 0 [0] |
| Gastritis erosive | 4 | 3 (1.2) [4] | 0 [0] | 0 [0] | 0 [0] |

n (%) = Number (%) of subjects reported ≥ 1 event of the preferred term. Events = total events within the group. Total Events = total events across all treatment groups. A subject was counted only once per preferred term for rate, but all events were included in the 'Events' column. Abbreviations: ES-combo = Eflornithine + Sulindac either co-formulated or co-administered; N or n = number Source: ISS SAP Table 5.2.1

**Table 51: Summary of TEAEs reported by ≥ 5.0% of subjects by duration of exposure**

| Preferred Term | ES-Combo 0–12 months Overall (N = 44) n (%) [Events] | ES-Combo 12–24 months Overall (N = 33) n (%) [Events] | ES-Combo 24–36 months Overall (N = 84) n (%) [Events] | ES-Combo > 36 months Overall (N = 82) n (%) [Events] |
|---|---|---|---|---|
| Subjects with > = 1 Event | 34 (77.3) [117] | 28 (84.8) [204] | 83 (98.8) [573] | 79 (96.3) [631] |
| Diarrhoea | 5 (11.4) [6] | 4 (12.1) [5] | 15 (17.9) [23] | 16 (19.5) [28] |
| Nausea | 5 (11.4) [5] | 8 (24.2) [10] | 6 (7.1) [8] | 6 (7.3) [10] |
| Constipation | 3 (6.8) [6] | 3 (9.1) [4] | 2 (2.4) [2] | 3 (3.7) [3] |
| Fatigue | 3 (6.8) [4] | 5 (15.2) [6] | 10 (11.9) [10] | 14 (17.1) [14] |
| Decreased appetite | 3 (6.8) [4] | 2 (6.1) [2] | 1 (1.2) [1] | 2 (2.4) [2] |
| Rectal haemorrhage | 3 (6.8) [3] | 1 (3.0) [1] | 6 (7.1) [6] | 6 (7.3) [7] |
| Rash | 3 (6.8) [3] | 2 (6.1) [2] | 4 (4.8) [4] | 6 (7.3) [6] |
| Abdominal pain | 2 (4.5) [3] | 3 (9.1) [6] | 8 (9.5) [10] | 7 (8.5) [12] |
| Influenza | 0 [0] | 5 (15.2) [5] | 6 (7.1) [7] | 5 (6.1) [5] |
| Ototoxicity | 2 (4.5) [2] | 5 (15.2) [5] | 18 (21.4) [22] | 14 (17.1) [16] |
| Urinary tract infection | 0 [0] | 4 (12.1) [4] | 4 (4.8) [4] | 2 (2.4) [2] |
| Arthralgia | 1 (2.3) [1] | 3 (9.1) [6] | 9 (10.7) [12] | 7 (8.5) [10] |
| Vomiting | 1 (2.3) [1] | 3 (9.1) [6] | 8 (9.5) [8] | 5 (6.1) [5] |
| Upper respiratory tract infection | 1 (2.3) [1] | 3 (9.1) [4] | 8 (9.5) [9] | 3 (3.7) [8] |
| Headache | 1 (2.3) [2] | 3 (9.1) [3] | 14 (16.7) [18] | 11 (13.4) [12] |
| Tinnitus | 1 (2.3) [1] | 3 (9.1) [3] | 5 (6.0) [5] | 7 (8.5) [7] |
| Abdominal pain upper | 1 (2.3) [1] | 3 (9.1) [3] | 7 (8.3) [8] | 8 (9.8) [10] |
| Sinusitis | 2 (4.5) [2] | 3 (9.1) [3] | 6 (7.1) [6] | 5 (6.1) [6] |
| Dizziness | 2 (4.5) [2] | 3 (9.1) [3] | 4 (4.8) [4] | 3 (3.7) [3] |
| Paraesthesia | 0 [0] | 2 (6.1) [3] | 4 (4.8) [5] | 5 (6.1) [5] |
| Nasopharyngitis | 0 [0] | 2 (6.1) [2] | 10 (11.9) [14] | 13 (15.9) [21] |
| Haematochezia | 1 (2.3) [1] | 2 (6.1) [2] | 4 (4.8) [6] | 6 (7.3) [9] |
| Weight decreased | 1 (2.3) [1] | 2 (6.1) [2] | 2 (2.4) [2] | 6 (7.3) [9] |
| Anxiety | 0 [0] | 2 (6.1) [2] | 2 (2.4) [2] | 0 [0] |
| Deafness | 0 [0] | 2 (6.1) [2] | 3 (3.6) [5] | 8 (9.8) [8] |
| Pneumonia | 0 [0] | 2 (6.1) [2] | 1 (1.2) [1] | 2 (2.4) [2] |
| Sinus congestion | 0 [0] | 2 (6.1) [2] | 3 (3.6) [3] | 1 (1.2) [1] |
| Balance disorder | 1 (2.3) [1] | 2 (6.1) [2] | 1 (1.2) [1] | 4 (4.9) [4] |
| Cough | 0 [0] | 2 (6.1) [2] | 2 (2.4) [2] | 7 (8.5) [8] |
| Hearing impaired | 0 [0] | 2 (6.1) [2] | 1 (1.2) [1] | 5 (6.1) [5] |
| Pyrexia | 0 [0] | 2 (6.1) [2] | 1 (1.2) [1] | 1 (1.2) [1] |
| Back pain | 2 (4.5) [2] | 1 (3.0) [3] | 11 (13.1) [11] | 13 (15.9) [19] |
| Haemoglobin decreased | 2 (4.5) [2] | 1 (3.0) [1] | 7 (8.3) [10] | 8 (9.8) [9] |
| Hypertension | 0 [0] | 1 (3.0) [1] | 6 (7.1) [6] | 7 (8.5) [10] |
| Pain in extremity | 0 [0] | 1 (3.0) [2] | 5 (6.0) [6] | 7 (8.5) [7] |
| Dyspnoea | 0 [0] | 1 (3.0) [1] | 5 (6.0) [6] | 3 (3.7) [5] |
| Myalgia | 0 [0] | 0 [0] | 5 (6.0) [5] | 4 (4.9) [4] |
| Gastrooesophageal reflux disease | 2 (4.5) [2] | 1 (3.0) [1] | 4 (4.8) [6] | 6 (7.3) [6] |
| Weight loss diet | 0 [0] | 0 [0] | 2 (2.4) [2] | 6 (7.3) [6] |
| Abdominal distension | 0 [0] | 1 (3.0) [1] | 1 (1.2) [2] | 6 (7.3) [6] |
| Dyspepsia | 0 [0] | 1 (3.0) [1] | 4 (4.8) [6] | 6 (7.3) [10] |
| Gastroenteritis | 0 [0] | 1 (3.0) [1] | 1 (1.2) [1] | 5 (6.1) [7] |
| Muscular weakness | 0 [0] | 0 [0] | 4 (4.8) [4] | 5 (6.1) [6] |
| Depression | 0 [0] | 1 (3.0) [1] | 1 (1.2) [1] | 5 (6.1) [5] |

Source: ISS SAP Table 5.2.7

**Safety Findings of the External Pharmacoprevention of Sporadic Colorectal Adenomas Study (PSCA) with an updated analysis study of the data (CAT 001)**

In order to align the adverse event review with the sponsor's most recently completed Phase 3 study CPP FAP-310, all treatment emergent adverse events were re-coded using MedDRA version 15.1. The analyses results identified in the SAP were the basis for the clinical study report CAT-001. Final report date: 29 May 2020.

For safety, recoding of AE data did not identify any additional safety concerns to those reported in the PSCA CSR.

Results from the report CAT-001 is presented here.

**Table 52: Summary of treatment emergent AEs (Safety Analysis Set) – PSCA study**

| | | Eflornithine + Sulindac (N = 188) | Placebo (N = 183) |
|---|---|---|---|
| **Analysis [1, 2]** | **Category** | **Subjects (%) [Events]** | **Subjects (%) [Events]** |
| Subjects with Reported ≥ 1 TEAE | | 172 (91.5) [1108] | 155 (84.7) [1011] |
| TEAE by Seriousness | Serious (SAE) | 43 (22.9) [62] | 31 (16.9) [41] |
| TEAE by Intensity | Mild | 157 (83.5) [866] | 141 (77.0) [812] |
| | Moderate | 82 (43.6) [168] | 69 (37.7) [137] |
| | Severe | 46 (24.5) [69] | 38 (20.8) [58] |
| | Missing Data | 3 (1.6) [5] | 4 (2.2) [4] |
| TEAE by Relationship | Not Related | 159 (84.6) [916] | 145 (79.2) [864] |
| | Related | 87 (46.3) [189] | 73 (39.9) [146] |
| | Missing Data | 2 (1.1) [3] | 1 (0.5) [1] |
| TEAE by Outcome | Resolved | 155 (82.4) [826] | 133 (72.7) [739] |
| | Resolved with Sequelae | 0 [0] | 0 [0] |
| | Not Resolved | 124 (66.0) [271] | 108 (59.0) [260] |
| | Unknown | 0 [0] | 0 [0] |
| | Death [3] | 2 (1.1) [2] | 1 (0.5) [1] |
| | Missing Data | 6 (3.2) [9] | 8 (4.4) [11] |
| TEAE by Action with Study Drug | Drug discontinued | 28 (14.9) [39] | 18 (9.8) [23] |
| Total Number of TEAE Per Subject [2] | n | 188 | 183 |
| | Mean (SD) | 5.9 (5.58) | 5.5 (5.92) |
| | Median | 4.0 | 4.0 |
| | Min, Max | 0, 32 | 0, 42 |

**Table 53: Summary of treatment emergent AEs by preferred term – Display of the most common events first for events reported by ≥ 10 subjects from either group and reported by ≥5.0% of subjects in either treatment group (Safety Analysis Set) – PSCA study**

| | | Eflornithine + Sulindac (N = 188) | Placebo (N = 183) |
|---|---|---|---|
| Adverse Event Preferred Term (MedDRA 15.1) | Total Events | Subjects (%) [Events] | Subjects (%) [Events] |
| Subjects with ≥ 1 Event | 2119 | 172 (91.5) [1108] | 155 (84.7) [1011] |
| Ototoxicity | 72 | 39 (20.7) [45] | 25 (13.7) [27] |
| Diarrhea | 98 | 33 (17.6) [54] | 25 (13.7) [44] |
| Fatigue | 50 | 28 (14.9) [29] | 20 (10.9) [21] |
| Headache | 48 | 21 (11.2) [24] | 16 (8.7) [24] |
| Arthralgia | 49 | 16 (8.5) [23] | 20 (10.9) [26] |
| Back pain | 48 | 22 (11.7) [27] | 14 (7.7) [21] |
| Hemoglobin decreased | 42 | 18 (9.6) [22] | 16 (8.7) [20] |
| Nasopharyngitis | 41 | 19 (10.1) [25] | 13 (7.1) [16] |
| Tinnitus | 35 | 14 (7.4) [14] | 15 (8.2) [21] |
| Abdominal pain upper | 30 | 12 (6.4) [14] | 13 (7.1) [16] |
| Nausea | 33 | 13 (6.9) [15] | 12 (6.6) [18] |
| Deafness | 27 | 12 (6.4) [14] | 12 (6.6) [13] |
| Dyspepsia | 33 | 9 (4.8) [13] | 15 (8.2) [20] |
| Abdominal pain | 31 | 12 (6.4) [18] | 11 (6.0) [13] |
| Hypertension | 27 | 12 (6.4) [15] | 10 (5.5) [12] |
| Pain in extremity | 25 | 12 (6.4) [14] | 8 (4.4) [11] |
| Paranesthesia | 24 | 11 (5.9) [13] | 9 (4.9) [11] |
| Sinusitis | 20 | 12 (6.4) [13] | 7 (3.8) [7] |
| Dizziness | 23 | 8 (4.3) [8] | 10 (5.5) [15] |
| Gastroesophageal reflux disease | 26 | 11 (5.9) [13] | 7 (3.8) [13] |
| Vomiting | 22 | 11 (5.9) [12] | 7 (3.8) [10] |
| Weight decreased | 21 | 10 (5.3) [13] | 8 (4.4) [8] |
| Upper respiratory tract infection | 21 | 7 (3.7) [8] | 10 (5.5) [13] |
| Influenza | 17 | 12 (6.4) [13] | 4 (2.2) [4] |

Gastrointestinal (3.5% of subjects) and cardiac disorders (2.2% of subjects) were the most commonly cited as AEs that led to study drug discontinuation.

Four deaths were reported in the PSCA CSR, however only one death occurred while a subject was on treatment. This event was coded by the preferred term of accidental death.

The causes of three post-study deaths were ruled unrelated to study intervention by the study investigators.

**Safety Findings of the Single Dose Crossover Study in Healthy Patients (CPP-P9-658)**

A total of 12 subjects were randomised in this study and all subjects received the 4 treatments under study.

No deaths, SAEs or severe TEAEs occurred in the study. No subject was withdrawn for safety reasons.

**Table 54: Overview of adverse events in CPP-P9-658**

| | ES-Co - Formulated (N=12) | Eflornithine (N=12) | Sulindac (N=12) | ES-Co-Administered (N=12) | Overall (N=12) |
|---|---|---|---|---|---|
| AEs reported (n) | | | | | 4 |
| TEAEs reported (n) | 2 | 0 | 1 | 1 | 4 |
| Subjects with at least one TEAE [n(%)] | 2 (17) | 0 | 1 (8) | 1 (8) | 4 (33) |
| Subjects with at least one drug-related TEAE [n(%)] | 1 (8) | 0 | 0 | 1 (8) | 2 (17) |
| TEAEs relationship | | | | | |
| Related [n(%)] | 1 (50) | 0 | 0 | 1 (100) | 2 (50) |
| Not Related [n(%)] | 1 (50) | 0 | 1 (100) | 0 | 2 (50) |
| TEAEs by severity/intensity | | | | | |
| Mild [n(%)] | 1 (50) | 0 | 1 (100) | 1 (100) | 3 (75) |
| Moderate [n(%)] | 1 (50) | 0 | 0 | 0 | 1 (25) |
| Severe [n(%)] | 0 | 0 | 0 | 0 | 0 |
| SAEs reported (n) | 0 | 0 | 0 | 0 | 0 |
| Subjects with at least one SAESAE [n(%)] | 0 | 0 | 0 | 0 | 0 |
| Subjects with at least one drug-related SAESAE [n(%)] | 0 | 0 | 0 | 0 | 0 |
| Deaths [n (%)] | 0 | 0 | 0 | 0 | 0 |

Source: Study CPP-P9-658, Table 14.3.1.1
Abbreviation: ES-Co-Administered = Eflornithine (3 x 250 mg tablets) + Sulindac (1 x 150 mg tablet) combination, ES-Co-Formulated = Eflornithine/Sulindac (2 x 375 mg/75 mg tablets), Eflornithine = eflornithine hydrochloride (HCl) monohydrate.

Dry mouth was reported following administration of co-administered eflornithine and sulindac, upper respiratory tract infection was reported following administration of sulindac, and vessel puncture site bruise and headache were each reported following administration of co-formulated eflornithine and sulindac.

There were 2 drug-related TEAEs reported (headache & dry mouth), 1 with co-formulated eflornithine and sulindac and 1 with co-administered eflornithine and sulindac; subjects dosed with sulindac or eflornithine did not experience any drug-related TEAEs.

## *Serious adverse event/deaths/other significant events*

**CPP FAP-310**

**Table 55: Summary of treatment-emergent SAEs (safety population)**

| System Organ Class | Combination N=56 | Sulindac N=57 | CPP-1X N=56 |
|---|---|---|---|
| Preferred Term | n (%) of Subjects | | |
| Subjects with at least 1 SAE | 11 (19.6) | 11 (19.3) | 14 (25.0) |
| Gastrointestinal disorders | 5 (8.9) | 5 (8.8) | 4 (7.1) |
| Small intestinal obstruction | 2 (3.6) | 2 (3.5) | 1 (1.8) |
| Abdominal pain | 1 (1.8) | 1 (1.8) | 0 |
| Ileus | 1 (1.8) | 0 | 1 (1.8) |
| Constipation | 0 | 0 | 1 (1.8) |
| Gastrointestinal haemorrhage | 0 | 1 (1.8) | 0 |
| Inguinal hernia | 1 (1.8) | 0 | 0 |
| Nausea | 0 | 1 (1.8) | 0 |
| Pancreatitis | 0 | 0 | 1 (1.8) |
| Pancreatitis acute | 1 (1.8) | 0 | 0 |
| Rectal haemorrhage | 0 | 1 (1.8) | 0 |
| Hepatobiliary disorders | 0 | 0 | 1 (1.8) |
| Biliary colic | 0 | 0 | 1 (1.8) |
| Injury, poisoning and procedural complications | 1 (1.8) | 3 (5.3) | 4 (7.1) |
| Alcohol poisoning | 0 | 0 | 1 (1.8) |
| Anastomotic stenosis | 0 | 1 (1.8) | 0 |
| Post procedural haemorrhage | 0 | 0 | 1 (1.8) |
| Postoperative ileus | 0 | 1 (1.8) | 0 |
| Procedural pain | 0 | 0 | 1 (1.8) |
| Seroma | 1 (1.8) | 0 | 0 |
| Upper limb fracture | 0 | 0 | 1 (1.8) |
| Wound complication | 0 | 1 (1.8) | 0 |
| Wound dehiscence | 1 (1.8) | 0 | 0 |
| Metabolism and nutrition disorders | 1 (1.8) | 0 | 0 |
| Hyperglycaemia | 1 (1.8) | 0 | 0 |

| System Organ Class<br>Preferred Term | Combination N=56 | Sulindac N=57 | CPP-1X N=56 |
|---|---|---|---|
| | n (%) of Subjects | | |
| Musculoskeletal and connective tissue disorders | 1 (1.8) | 1 (1.8) | 0 |
| Bursitis | 1 (1.8) | 0 | 0 |
| Intervertebral disc protrusion | 0 | 1 (1.8) | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 1 (1.8) | 0 | 3 (5.4) |
| Chronic myeloid leukaemia | 0 | 0 | 1 (1.8) |
| Lung adenocarcinoma | 1 (1.8) | 0 | 0 |
| Renal cell carcinoma | 0 | 0 | 1 (1.8) |
| Thyroid neoplasm | 0 | 0 | 1 (1.8) |
| Nervous system disorders | 0 | 0 | 2 (3.6) |
| Cerebrovascular accident | 0 | 0 | 1 (1.8) |
| Migraine | 0 | 0 | 1 (1.8) |
| Pregnancy, puerperium and perinatal conditions | 0 | 1 (1.8) | 0 |
| Abortion spontaneous | 0 | 1 (1.8) | 0 |
| Psychiatric disorders | 1 (1.8) | 1 (1.8) | 0 |
| Depression | 0 | 1 (1.8) | 0 |
| Psychotic disorder | 1 (1.8) | 0 | 0 |
| Renal and urinary disorders | 2 (3.6) | 0 | 0 |
| Nephritis | 1 (1.8) | 0 | 0 |
| Renal failure acute | 1 (1.8) | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | 1 (1.8) | 0 | 1 (1.8) |
| Chronic obstructive pulmonary disease | 0 | 0 | 1 (1.8) |
| Pulmonary mass | 1 (1.8) | 0 | 0 |
| Vascular disorders | 0 | 1 (1.8) | 0 |
| Deep vein thrombosis | 0 | 1 (1.8) | 0 |

SAE=serious adverse event
Source: Table 14.3.2.1

There were no TEAEs leading to death reported during the study.

A similar percentage of subjects experienced treatment-emergent SAEs across treatment groups (range: 19.3% to 25.0%).

**Table 56: Subjects with Treatment-related treatment-emergent SAEs (safety population)**

| Subject Number | Preferred Term | Start Day/ End Day | Toxicity Grade | Relationship | Outcome | Action Taken with Study Drug |
|---|---|---|---|---|---|---|
| **Combination treatment group** | | | | | | |
| 103123 | Nephritis | 183/241 | 2 | Possibly related | Resolved | Drug withdrawn |
| 110025 | Psychotic disorder | 708/ ongoing | 2 | Possibly related | Not resolved | Dose not changed |
| 122194 | Pancreatitis acute | 369/590 | 3 | Possibly related | Resolved with sequelae | Drug interrupted |
| **Sulindac treatment group** | | | | | | |
| 101250 | Nausea | 119/193 | 3 | Possibly related | Resolved | Dose not changed |
| 102035 | Deep vein thrombosis | 239/448 | 2 | Probably related | Resolved | Drug withdrawn |
| 111086 | Depression | 54/ ongoing | 3 | Possibly related | Not resolved | Multiple |
| 111117 | Abortion spontaneous | 438/438 | 2 | Possibly related | Resolved | -- |
| **CPP-1X treatment group** | | | | | | |
| 110182 | Cerebrovascular accident | 760/762 | 3 | Possibly related | Resolved | Drug withdrawn |

SAE=serious adverse event
Source: Listing 16.2.7.2

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.

***Adverse Events of Special Interest***

**CPP-FAP-310**

Standardised MedDRA queries were used for analysis of TEAEs based on adverse events of special interest identified in the protocol (gastrointestinal, hearing, and cardiovascular/thrombotic), which were based on the known toxicities of the single agents. Several additional adverse events of special interest were identified and are also known toxicities for the single agents (anaphylactic reaction, haematopoietic cytopoenia, depression). Patients with FAP are at risk for extra colonic malignancies, so these were also evaluated.

- Cardiovascular, Embolic, and Thrombotic TEAEs

One subject in each treatment group experienced an embolic or thrombotic TEAE; a different TEAE (preferred term) was experienced in each treatment group. One subject in the CPP-1X treatment group experienced 2 cerebrovascular events, the second of which led to premature discontinuation of study drug. The deep vein thrombosis was an SAE considered by the investigator to be probably related to study drug and that resulted in premature discontinuation of study drug.

**Table 57: Summary of Cardiovascular, Embolic and thrombotic TEAEs (Safety population)**

| SMQ Category | Combination N=56 | Sulindac N=57 | CPP-1X N=56 |
|---|---|---|---|
| Preferred Term | n (%) of Subjects | | |
| Embolic and thrombotic events | 1 (1.8) | 1 (1.8) | 1 (1.8) |
| Cerebrovascular accident | 0 | 0 | 1 (1.8) |
| Deep vein thrombosis | 0 | 1 (1.8) | 0 |
| Retinal vein thrombosis | 1 (1.8) | 0 | 0 |
| Cerebrovascular disorders | 0 | 0 | 1 (1.8) |
| Cerebrovascular accident | 0 | 0 | 1 (1.8) |

SMQ=standardised Medical Dictionary for Regulatory Activities query
Source: Table 14.3.2.3

Fourteen (14)% of participants in the pivotal study had hypertension as part of their medical history which was balanced between the 3 arms. There were no concerning reports of hypertension as a vascular disorder in the pivotal study (4 patients overall, none were SAEs).

- Anaphylactic Reaction TEAEs

The percentage of subjects with at least 1 TEAE coding to the anaphylactic reaction SMQ was highest in the combination treatment group (26.8%), followed by the sulindac treatment group (22.8%) and the CPP-1X treatment group (14.3%). Rash, rash pruritic, erythema, lip oedema, and urticaria contributed to the higher percentage in the combination treatment group compared with either single-agent treatment group. No TEAE coding to the anaphylactic reaction SMQ was an SAE.

**Table 58: Summary of anaphylactic reaction TEAEs (Safety population)**

| SMQ Category | Combination N=56 | Sulindac N=57 | CPP-1X N=56 |
|---|---|---|---|
| Preferred Term | n (%) of Subjects | | |
| Anaphylactic reaction | 15 (26.8) | 13 (22.8) | 8 (14.3) |
| Asthma | 0 | 0 | 1 (1.8) |
| Chest discomfort | 1 (1.8) | 1 (1.8) | 0 |
| Cough | 3 (5.4) | 4 (7.0) | 6 (10.7) |
| Dyspnoea | 0 | 2 (3.5) | 0 |
| Erythema | 1 (1.8) | 0 | 0 |
| Flushing | 0 | 1 (1.8) | 0 |
| Lip oedema | 1 (1.8) | 0 | 0 |
| Pruritus | 3 (5.4) | 4 (7.0) | 2 (3.6) |
| Rash | 6 (10.7) | 2 (3.5) | 0 |
| Rash pruritic | 2 (3.6) | 0 | 1 (1.8) |
| Urticaria | 3 (5.4) | 0 | 0 |

SMQ=standardised Medical Dictionary for Regulatory Activities query
Source: Table 14.3.2.3

- Hearing and Vestibular Disorders TEAEs

**Table 59: Summary of Hearing and Vestibular Disorders TEAEs (Safety population)**

| SMQ Category | Combination N=56 | Sulindac N=57 | CPP-1X N=56 |
|---|---|---|---|
| Preferred Term | n (%) of Subjects | | |
| Hearing and vestibular disorders | 8 (14.3) | 11 (19.3) | 11 (19.6) |
| Deafness | 1 (1.8) | 0 | 0 |
| Deafness bilateral | 0 | 0 | 1 (1.8) |
| Deafness neurosensory | 1 (1.8) | 1 (1.8) | 0 |
| Dizziness | 4 (7.1) | 4 (7.0) | 6 (10.7) |
| Eustachian tube dysfunction | 0 | 1 (1.8) | 2 (3.6) |
| Hearing impaired | 1 (1.8) | 2 (3.5) | 0 |
| Tinnitus | 2 (3.6) | 6 (10.5) | 1 (1.8) |
| Vertigo | 0 | 0 | 1 (1.8) |
| Vertigo positional | 0 | 0 | 1 (1.8) |

SMQ=standardised Medical Dictionary for Regulatory Activities query
Source: Table 14.3.2.3

No TEAE coding to the hearing and vestibular disorders SMQ was an SAE. The deafness bilateral and 1 TEAE of hearing impaired (sulindac treatment group) resulted in premature discontinuation of study drug.

- Gastrointestinal Perforation, Ulceration, Haemorrhage, or Obstruction TEAEs

**Table 60: Summary of Gastrointestinal perforation, Ulceration, Haemorrhage or Obstruction TEAEs (Safety population)**

| SMQ Category | Combination N=56 | Sulindac N=57 | CPP-1X N=56 |
|---|---|---|---|
| Preferred Term | n (%) of Subjects | | |
| Gastrointestinal perforation, ulceration, hemorrhage, or obstruction | 20 (35.7) | 23 (40.4) | 15 (26.8) |
| Abdominal discomfort | 0 | 2 (3.5) | 2 (3.6) |
| Anal fistula | 1 (1.8) | 0 | 1 (1.8) |
| Anal haemorrhage | 0 | 2 (3.5) | 1 (1.8) |
| Anastomotic stenosis | 0 | 1 (1.8) | 1 (1.8) |
| Anastomotic ulcer | 0 | 2 (3.5) | 1 (1.8) |
| Diarrhoea haemorrhagic | 1 (1.8) | 0 | 0 |
| Duodenal ulcer | 1 (1.8) | 0 | 0 |
| Gastric ulcer | 1 (1.8) | 2 (3.5) | 0 |
| Gastric ulcer helicobacter | 1 (1.8) | 0 | 0 |
| Gastritis erosive | 3 (5.4) | 0 | 0 |
| Gastrointestinal erosion | 0 | 1 (1.8) | 0 |
| Gastrointestinal haemorrhage | 0 | 1 (1.8) | 0 |
| Gastrointestinal pain | 0 | 1 (1.8) | 0 |
| Haematochezia | 6 (10.7) | 2 (3.5) | 6 (10.7) |
| Haemorrhoidal haemorrhage | 0 | 1 (1.8) | 0 |
| Ileal ulcer | 0 | 1 (1.8) | 1 (1.8) |
| Ileus | 1 (1.8) | 0 | 2 (3.6) |
| Impaired gastric emptying | 0 | 1 (1.8) | 0 |
| Intestinal obstruction | 0 | 1 (1.8) | 0 |
| Peptic ulcer | 1 (1.8) | 0 | 0 |
| Postoperative ileus | 0 | 1 (1.8) | 0 |
| Rectal haemorrhage | 7 (12.5) | 7 (12.3) | 4 (7.1) |
| Rectal ulcer | 0 | 1 (1.8) | 0 |
| Small intestinal bacterial overgrowth | 0 | 1 (1.8) | 0 |
| Small intestinal obstruction | 3 (5.4) | 2 (3.5) | 1 (1.8) |
| Upper gastrointestinal haemorrhage | 0 | 1 (1.8) | 0 |

SMQ=standardised Medical Dictionary for Regulatory Activities query
Source: Table 14.3.2.3

Treatment-emergent SAEs included

- gastrointestinal haemorrhage (n=1 sulindac treatment group),
- ileus (n=1 combination treatment group & n=1 CPP-1X treatment group),
- rectal haemorrhage (n=1 sulindac treatment group),
- small intestinal obstruction (n=2 combination treatment group, n=2 sulindac treatment group & n=1 CPP-1X treatment group).

None of these SAEs was considered by the investigator to be related to study drug.

One TEAE of haematochezia (CPP-1X treatment group) and 1 TEAE of peptic ulcer (combination treatment group) resulted in premature discontinuation of study drug.

- Haematopoietic Cytopoenias TEAEs

**Table 61: Summary of haematopoietic cytopenias TEAEs (safety population)**

| SMQ Category | Combination N=56 | Sulindac N=57 | CPP-1X N=56 |
|---|---|---|---|
| Preferred Term | n (%) of Subjects | | |
| Hematopoietic cytopenias | 1 (1.8) | 5 (8.8) | 3 (5.4) |
| Anaemia | 1 (1.8) | 2 (3.5) | 1 (1.8) |
| Haematocrit decreased | 0 | 0 | 1 (1.8) |
| Haemoglobin decreased | 0 | 0 | 1 (1.8) |
| Platelet count decreased | 0 | 3 (5.3) | 1 (1.8) |
| Red blood cell count decreased | 0 | 0 | 1 (1.8) |
| White blood cell count decreased | 0 | 1 (1.8) | 0 |

SMQ=standardised Medical Dictionary for Regulatory Activities query

None of these events were SAEs or resulted in premature discontinuation of study drug.

- Gastrointestinal Nonspecific Inflammation and Dysfunctional Conditions TEAEs

Gastrointestinal Nonspecific Inflammation and Dysfunctional Conditions TEAEs occurred with similar percentage cross treatment groups. The percentage of subjects experiencing abdominal pain upper was higher in the combination treatment group (12.5%) compared with the sulindac (1.8%) and CPP-1X (7.1%) treatment groups. Erosive gastritis only occurred in the combination arm n=2. None of these TEAEs resulted in premature discontinuation of study drug. Treatment-emergent SAEs included abdominal pain (n=1 combination treatment group; n=1 sulindac treatment group), constipation (n=1 CPP-1X treatment group), and nausea (n=1 sulindac treatment group).

- Depression and Suicide/Self-Injury and Psychosis and Psychotic Disorders TEAEs

**Table 62: Summary of depression and suicide/self-injury and Psychosis and Psychotic disorders TEAEs (safety population)**

| SMQ Category | Combination N=56 | Sulindac N=57 | CPP-1X N=56 |
|---|---|---|---|
| Preferred Term | n (%) of Subjects | | |
| Depression and suicide/self-injury | 3 (5.4) | 9 (15.8) | 5 (8.9) |
| Adjustment disorder with mixed anxiety and depressed mood | 1 (1.8) | 0 | 0 |
| Depressed mood | 0 | 1 (1.8) | 1 (1.8) |
| Depression | 1 (1.8) | 4 (7.0) | 1 (1.8) |
| Depressive symptom | 0 | 1 (1.8) | 0 |
| Disturbance in attention | 0 | 3 (5.3) | 0 |
| Major depression | 1 (1.8) | 0 | 0 |
| Memory impairment | 0 | 0 | 2 (3.6) |
| Mood swings | 0 | 0 | 1 (1.8) |
| Psychomotor hyperactivity | 0 | 1 (1.8) | 0 |
| Psychosis and psychotic disorders | 2 (3.6) | 0 | 0 |
| Major depression | 1 (1.8) | 0 | 0 |
| Psychotic disorder | 1 (1.8) | 0 | 0 |

SMQ=standardised Medical Dictionary for Regulatory Activities query
Source: Table 14.3.2.3

Treatment-emergent adverse events that were SAEs included depression (n=1 sulindac treatment group) and psychotic disorder (n=1 combination treatment group). Both of these SAEs were considered by the investigator to be possibly related to study drug.

The SAE of depression (n=1 sulindac treatment group) and 1 TEAE of depressive symptom (n=1 sulindac treatment group) resulted in premature discontinuation of study drug.

- Malignancies TEAEs

**Table 63: Summary of malignancies TEAEs (Safety population)**

| SMQ Category | Combination N=56 | Sulindac N=57 | CPP-1X N=56 |
|---|---|---|---|
| Preferred Term | n (%) of Subjects | | |
| Malignancies | 2 (3.6) | 2 (3.5) | 4 (7.1) |
| Basal cell carcinoma | 0 | 1 (1.8) | 0 |
| Chronic myeloid leukaemia | 0 | 0 | 1 (1.8) |
| Gastric cancer | 1 (1.8) | 0 | 0 |
| Lung adenocarcinoma | 1 (1.8) | 0 | 0 |
| Neoplasm | 0 | 0 | 1 (1.8) |
| Renal cell carcinoma | 0 | 0 | 1 (1.8) |
| Squamous cell carcinoma | 0 | 1 (1.8) | 0 |
| Thyroid neoplasm | 0 | 0 | 1 (1.8) |
| Vulval cancer stage 0 | 0 | 0 | 1 (1.8) |

SMQ=standardised Medical Dictionary for Regulatory Activities query
Source: Table 14.3.2.3

The SAEs of chronic myeloid leukaemia (n=1) and lung adenocarcinoma (n=1) and the non-serious gastric cancer (n=1) resulted in premature discontinuation of study drug. Other SAEs were renal cell carcinoma (n=1) and thyroid neoplasm (n=1). Each of the TEAEs were considered unrelated to study drug by the investigator.

**PSCA study**

The eflornithine + sulindac arm had a higher rate of balance disorder or vertigo under the SMQ of hearing and vestibular events, a higher rate of dyspnoea and asthma in the anaphylactic reaction SMQ, a higher rate of myocardial infarction and coronary artery bypass in the thrombotic and embolic SMQ. There was also an increase in rectal haemorrhage, haematochezia, gastrointestinal haemorrhage, and haemorrhoidal haemorrhage in the gastrointestinal perforation, ulceration, haemorrhage, or obstruction SMQ, an increase the number of haemoglobin decreased, anaemia, and white blood cell count (decreased) events in the haematopoietic cytopoenias SMQ, and an increase in diarrhoea, gastroesophageal reflux disease, vomiting, constipation, and abdominal distension in the gastrointestinal nonspecific inflammation and dysfunctional conditions SMQ.

An analysis of cardiovascular risk factors demonstrated that the eflornithine + sulindac arm had a higher proportion of subjects with cardiovascular risk factors which may account for the higher rate of myocardial infarctions. When the higher risk subjects were excluded, the rates of cardiovascular events were comparable to the placebo group.

## *Laboratory findings*

CPP FAP-310

A total of 29 subjects (8 combination treatment group, 10 sulindac treatment group, 11 CPP-1X treatment group) had at least 1 clinically significant laboratory abnormality during the study. Of these subjects, 3 subjects (2 in the combination treatment group and 1 in the sulindac treatment group) experienced TEAEs resulting in study drug discontinuation. In addition, 1 subject in the combination treatment group experienced a treatment-emergent SAE of hyperglycaemia concurrent with an SAE of pancreatitis acute

One Subject from the combination treatment group experienced a nonserious TEAE of hepatic enzyme increased approximately 2 years after starting study drug that resulted in study drug discontinuation. The event was ongoing and considered possibly related to study drug by the investigator.

One Subject from the combination treatment group) experienced nonserious TEAEs of blood creatinine increased and proteinuria and an SAE of nephritis approximately 6 months after starting study drug. The subject was not hospitalised or treated for this SAE, but was discontinued from study by recommendation of her nephrologist who advised her not to take NSAIDs. The events lasted approximately 2 months.

One subject from the combination treatment group experienced an SAE of hyperglycaemia that began approximately 13 months after the start of study drug that was considered unrelated to study drug by the investigator. The event was considered resolved with the sequela of diabetes mellitus, likely secondary to pancreatitis, a serious TEAE that was considered possibly related to study drug by the investigator and that had begun approximately 1 month prior to the hyperglycaemia.

One Subject from the sulindac treatment group) experienced nonserious TEAEs of alanine aminotransferase increased and gamma-glutamyl transferase increased approximately 2 years after starting study drug that resulted in study drug discontinuation, but that were considered unrelated to study drug by the investigator. The events lasted approximately 2 months.

Electrocardiogram

Three subjects had abnormal, clinically significant ECG findings as follows and none of the 3 needed to discontinue treatment for the abnormality:

- One subject from the CPP-1X treatment group at Month 3 (predose) and Month 3 (4 hours post-dose): a nonserious TEAE of electrocardiogram abnormal was recorded for this subject
- One Subject from the sulindac treatment group at Month 6: a nonserious TEAE of electrocardiogram abnormal was recorded for this subject
- One subject from the combination treatment group at Month 24/end of initial treatment: a nonserious TEAE of atrial fibrillation was recorded for this subject

Audiometry

**Table 64: Summary of CTCAE grade 1 or higher hearing loss for all subjects (safety population)**

| Subject Number | Baseline | Month 6 | Month 12 | Month 24 | Month 30 | Month 36 | Month 42 | Month 48 |
|---|---|---|---|---|---|---|---|---|
| **Combination treatment group** | | | | | | | | |
| 101166 | 0 | N/A | **Grade 1** | 0 | N/A | 0 | | |
| 104041 | 0 | N/A | 0 | 0 | N/A | **Grade 1** | N/A | **Grade 1** |
| 111103 | 0 | N/A | 0 | **Grade 1** | N/A | 0 | 0 | |
| 111174[a] | 0 | N/A | 0 | 0 | **Grade 1** | | | |
| 115078 | 0 | N/A | 0 | 0 | 0 | 0 | 0 | **Grade 1** |
| 122228 | 0 | N/A | 0 | **Grade 1** | 0 | | | |
| 124222 | 0 | N/A | **Grade 1** | 0 | 0 | | | |
| **Sulindac treatment group** | | | | | | | | |
| 111095 | 0 | N/A | 0 | 0 | N/A | **Grade 1** | **Grade 1** | |
| 113227 | 0 | N/A | 0 | **Grade 1** | 0 | | | |
| **CPP-1X treatment group** | | | | | | | | |
| 111104 | 0 | N/A | **Grade 1** | | | | | |
| 115074[b] | 0 | **Grade 1** | | | | | | |
| 116044[c] | 0 | N/A | **Grade 1** | | | | | |

CTCEAE=Common Terminology Criteria for Adverse Event; N/A=not available
Shaded cells indicate subject was no longer receiving study drug.
[a] Month 30 is captured as Month 36 in Table 14.3.10.1 and Table 14.3.10.2.
[b] Month 6 is captured as Month 24 in Table 14.3.10.1 and Table 14.3.10.2.
[c] The screening/baseline assessment was outside of the protocol-specified window; therefore, no change from baseline results were programmed in the listing.
Source: Listing 16.2.8.6

Eleven subjects met the Grade 1 definition (change from baseline of ≥15 decibels at 2 consecutive frequencies). No subject met the requirements for Grade 2 hearing loss, which corresponds to >25 dB at 2 contiguous frequencies or any higher grade. A higher number of subjects experienced a Grade 1 audiometric change in the combination treatment group (n=7) compared with the CPP-1X treatment group (n=3) or the sulindac treatment group (n=2). Five (4 combination treatment group, 1 sulindac treatment group) subjects had temporary impairments by audiometry that improved while on study.

CPP-P9-658

All the abnormal clinical laboratory values were marginally higher or lower than their reference ranges and none were considered clinically significant by the investigator. There were no clinically significant abnormalities in the vital signs and ECGs of the subjects in this study. All physical examinations were judged normal.

## *Safety in special populations*

Intrinsic Factors

Age, Sex, Race

Eligibility requirement of this section is age ≥ 18; sex and race are not limiting.

Renal Insufficiency

Eligibility requirement of this section is renal status indicated creatinine no greater than 1.5 × ULN within 30 days prior to randomisation.

Paediatric Population

In this study, the primary inclusion criterion is male and female subjects ≥18 years of age. The drug was not tested for the paediatric population.

Extrinsic Factors

Subjects were instructed to not take the following medications or supplements while taking the study drug: oral corticosteroids (such as prednisone), cyclosporine, NSAIDs (such as ibuprofen, celecoxib, and aspirin in excess of 100 mg daily or 700 mg weekly), diflunisal, supplements containing omega-3-fatty acids (such as fish oil), anticoagulants (such as warfarin, Pradaxa, Eliquis, Plavix, and other direct thrombin inhibitors), fluconazole, lithium, furosemide and thiazides, dimethylsulfoxide, methotrexate, probenecid, propoxyphene hydrochloride, Tylenol (acetaminophen) preparations containing aspirin or cytotoxic chemotherapy drugs, or other FAP directed drug therapy.

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

If the dose was missed, the tablets may have been taken with the midday or evening meal. If an entire day was missed, this was to be indicated in the weekly dose accountability in the diary, but double-dosing the following day was not allowed. If the subject vomited within an hour after taking the tablets, the subject was to record a missed dose in the diary. If the subject vomited more than 1 hour after taking the tablets, the dose was not considered missed. In either case, no additional tablets were to be taken until the scheduled dose the next day. Any unused study drug was to be returned at the subject's next scheduled visit and an accounting of the study drug was performed and recorded by the research nurse or other qualified individual.

Drug Interactions

This study allowed for the use of aspirin of 81 – 100 mg daily to a maximum of 700 mg weekly.

Use in Pregnancy and Lactation

Eflornithine is known to be embryotoxic in animal studies and is listed as a safety risk in the Investigator's Brochure. 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 (Lopez-Garcia et al. 2008). 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.

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.) for additional information (Balmana et al. 2013).

One subject in this study had a positive pregnancy test and stopped study medication upon confirmation. One subject in the combination treatment group experienced a positive serum pregnancy test during the study (Day 543). Study drug was stopped (last dose before positive pregnancy test was on Day 542). The subject underwent a planned abortion (preferred term: abortion induced) on Day 560. Study drug was restarted on Day 575 and the last dose of study drug was taken on Day 1096.

Although no positive serum pregnancy tests were recorded, an additional subject in the sulindac treatment group had a confirmed pregnancy on Day 384; the last dose of study drug was taken on Day 384. The subject experienced an SAE of abortion spontaneous on Day 438 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.

In addition, the female partner of each of 3 male subjects became pregnant and delivered live infants without problems or complications.

Overdose

No overdose was recorded with the controlled doses administered.

Drug Abuse

From the study, there is no evidence to suggest the drug can create a dependence in humans.

Withdrawal and Rebound

From the study, there is no evidence to suggest the drug can create withdrawal and rebound symptoms in humans.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

This study did not comment nor suggest restrictions on driving or the operation of equipment though dizziness, vertigo and fatigue have been reported as treatment-related TEAEs.

## *Safety related to drug-drug interactions and other interactions*

No drug-drug or other drug-disease interactions were planned or performed.

## *Discontinuation due to adverse events*

CPP FAP-310

Nine (16.1%) subjects in the combination treatment group, 6 (10.5%) subjects in the sulindac treatment group, and 5 (8.9%) subjects in the CPP-1X treatment group experienced at least 1 TEAE leading to discontinuation of study drug. Hypersensitivity (2 [3.6%] subjects in the combination treatment group) was the only TEAE that led to premature discontinuation of study drug in >1 subject in a treatment group.

**Table 65: Subjects with TEAEs leading to discontinuation of study drug (safety population)**

| Subject Number | Preferred Term | Start Day/ End Day | Toxicity Grade | Relationship | Outcome |
|---|---|---|---|---|---|
| **Combination treatment group** | | | | | |
| 101137 | Lung adenocarcinoma[a] | 164/ ongoing | 4 | Unrelated | Not resolved |
| 101248 | Hepatic enzyme increased | 732/ ongoing | 1 | Possibly related | Not resolved |
| | Hepatic steatosis | 752/ ongoing | 1 | Possibly related | Not resolved |
| 102110 | Decreased appetite | 1150/ ongoing | 1 | Possibly related | Resolved |
| | Peptic ulcer | 1150/1171 | 2 | Probably related | Resolved |
| 102216 | Hypersensitivity | 68/72 | 1 | Definitely related | Resolved |
| 103123 | Blood creatinine increased | 183/241 | 2 | Probably related | Resolved |
| | Nephritis[a] | 183/241 | 2 | Possibly related | Resolved |
| | Proteinuria | 183/241 | 2 | Probably related | Resolved |
| 104115 | Gastric cancer | 313/ ongoing | 2 | Unrelated | Not resolved |
| 108124 | Hypersensitivity | 20/26 | 2 | Probably related | Resolved |
| 110119 | Drug hypersensitivity | 27/29 | 2 | Definitely related | Resolved |
| 118146 | Rash | 44/60 | 1 | Definitely related | Resolved |
| **Sulindac treatment group** | | | | | |
| 102035 | Deep vein thrombosis[a] | 239/448 | 2 | Probably related | Resolved |
| 108206 | Glomerulonephropathy | 190/ ongoing | 3 | Possibly related | Not resolved |
| 108226 | Depressive symptom | 76/228 | 1 | Possibly related | Resolved |
| 111086 | Depression[a] | 54/ongoing | 3 | Possibly related | Not resolved |
| 113189 | Hearing impaired | 6/ongoing | 1 | Possibly related | Not resolved |
| 119164 | Alanine aminotransferase increased | 705/773 | 1 | Unrelated | Resolved |
| | Gamma-glutamyltransferase increased | 705/791 | 1 | Unrelated | Resolved |
| **CPP-1X treatment group** | | | | | |
| 110182 | Cerebrovascular accident[a] | 760/762 | 3 | Possibly related | Resolved |
| 111104 | Deafness bilateral | 373/ ongoing | 1 | Probably related | Not resolved |
| 111170 | Pancreatitis[a] | 32/112 | 4 | Unrelated | Resolved |
| 111204 | Haematochezia | 29/ongoing | 2 | Probably related | Not resolved |
| | Anastomotic stenosis | 44/ongoing | 3 | Possibly related | Not resolved |
| 115038 | Chronic myeloid leukaemia[a] | 952/ ongoing | 3 | Unrelated | Not resolved |

TEAE=treatment-emergent adverse event
[a] Serious adverse event.

## *Post marketing experience*

Post-marketing data and recent literature were evaluated for the clinical safety of eflornithine and sulindac. The 2 post-marketing databases that were analysed were the FDA's FAERS Dashboard and WHO's VigiAccess™ platforms; PubMed was used to search the clinical literature.

FAERS

The FDA's Adverse Event Reporting System (FAERS) Public Dashboard was reviewed for adverse events reported for eflornithine and sulindac products. The FAERS database contains adverse events voluntarily reported to the FDA each quarter. Since the FAERS database contains voluntary reports from populations of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure. Additionally, the FAERS Dashboard does not provide information regarding the route of administration of the product (unless the proprietary product name is listed), or if the treatment is considered the primary suspect for the adverse event.

WHO

The World Health Organization's VigiBase was searched for adverse events reported for eflornithine and sulindac products. VigiBase is the largest and most comprehensive pharmacovigilance database worldwide, reporting adverse events since 1968. However, reports to VigiBase are voluntary, therefore causal relationships cannot be made. In April 2015, WHO launched VigiAcess, to provide open access to adverse events summary statistics. WHO and FAERS may report overlapping events, however, the extent of overlap between these databases has not been assessed.

Eflornithine

In the VigiAcess™ database, eflornithine products were not characterised by formulation or route of administration; all eflornithine-containing products are listed in the same search result. When searched for "Ornidyl" or "Vaniqa", VigiAcess™ retrieves adverse events identical to "eflornithine". The VigiAcess™ database was searched for "eflornithine"; reported adverse events and summary statistic information for these products are summarised below.

A total of 1963 events representing 857 records were reported for eflornithine-containing products. While severity of adverse event and patient outcome are not reported in VigiAcess™, adverse events are categorised by adverse drug reaction type.

**Table 66: Adverse event categories reported for eflornithine products**

| Category | Number of Events |
|---|---|
| Blood and lymphatic system disorders | 3 |
| Cardiac disorders | 10 |
| Ear and labyrinth disorders | 24 |
| Eye disorders | 18 |
| Gastrointestinal disorders | 388 |
| General disorders and administration site conditions | 365 |
| Hepatobiliary disorders | 1 |
| Immune system disorders | 4 |
| Infections and infestations | 26 |
| Injury, poisoning and procedural complications | 60 |
| Investigations | 7 |
| Metabolism and nutrition disorders | 85 |
| Musculoskeletal and connective tissue disorders | 152 |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | 4 |
| Nervous system disorders | 324 |
| Pregnancy, puerperium and perinatal conditions | 3 |
| Product issues | 54 |
| Psychiatric disorders | 116 |
| Renal and urinary disorders | 14 |
| Reproductive system and breast disorders | 4 |
| Respiratory, thoracic and mediastinal disorders | 30 |
| Skin and subcutaneous tissue disorders | 243 |
| Surgical and medical procedures | 1 |
| Vascular disorders | 27 |
| **Total** | **1963*** |

*Represents multiple events for each record. Each event can count in multiple categories

Sulindac

A total of 10,199 events representing 6177 records were reported for sulindac-containing products. While severity of adverse event and patient outcome are not reported in VigiAcess, adverse events are categorised by adverse drug reaction type.

**Table 67: Adverse event categories reported for sulindac products**

| Category | Number of Events |
|---|---|
| Blood and lymphatic system disorders | 676 |
| Cardiac disorders | 167 |
| Congenital, familial and genetic disorders | 10 |
| Ear and labyrinth disorders | 120 |
| Endocrine disorders | 14 |
| Eye disorders | 250 |
| Gastrointestinal disorders | 1826 |
| General disorders and administration site conditions | 1111 |
| Hepatobiliary disorders | 718 |
| Immune system disorders | 333 |
| Infections and infestations | 218 |
| Injury, poisoning and procedural complications | 60 |
| Investigations | 376 |

| | |
|---|---|
| Metabolism and nutrition disorders | 208 |
| Musculoskeletal and connective tissue disorders | 209 |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | 33 |
| Nervous system disorders | 633 |
| Pregnancy, puerperium and perinatal conditions | 6 |
| Product issues | 4 |
| Psychiatric disorders | 288 |
| Renal and urinary disorders | 492 |
| Reproductive system and breast disorders | 62 |
| Respiratory, thoracic and mediastinal disorders | 304 |
| Skin and subcutaneous tissue disorders | 1774 |
| Social circumstances | 5 |
| Surgical and medical procedures | 11 |
| Vascular disorders | 291 |
| **Total** | **10,199*** |

*Represents multiple events for each record. Each event can count in multiple categories

## 2.6.1. Discussion on clinical safety

Neither mono-components have well established clinical utility in the applied condition and would not be considered standard treatments. Therefore, comparing the safety of the FDC versus each mono-component is not informative for FAP specifically. While there is experience of use with sulindac as an NSAID, it is recommended for short term use only. There is very limited experience of eflornithine administered systemically given that this active substance is being used in the EU as a topical cream for hirsutism.

The summary of safety from clinical trials assessing sulindac alone and eflornithine either alone or in combination with other agents were submitted in order to support that sulindac and eflornithine are well established medicinal products. While literature reviews can be supportive, they cannot be used to confirm 'well-established use', as per the regulatory definition as neither mono-components have an approved chemoprevention indication for FAP.

Study CPP-FAP-310 study was not powered for adverse event comparison. Information on exposure to Flynpovi expressed in patient-years was provided as per the recommendations of ICH E1 given that the number of patients receiving treatment reduced greatly after 2 years. For the CPP FAP-310 study, the exposure to the eflornithine/sulindac combination was 108.9 patient years. For the PSCA study, the exposure to eflornithine/sulindac combination was 402.6 patient years.

In study CPP-FAP 310, the most common SOC was gastrointestinal disorders for all three treatment groups, with the combination having the highest percentage of subjects at 71.4%, followed by eflornithine with 62.5%, and sulindac at 61.4%. The combination arm also had a higher percentage of subjects with skin and subcutaneous disorder events at 35.7% of subjects as compared to eflornithine at 25.0% and sulindac at 21.1%. Eye disorder events were also higher in the combination arm at 10.7% as compared to 3.6% of subjects in the eflornithine arm and 3.5% in the sulindac arm. Immune system disorder events had a higher percentage in the combination arm at 8.9% of subjects compared to 5.4% of eflornithine treated subjects and 1.8% of sulindac treated subjects. Cardiac disorders had a higher percentage of subjects in the combination arm (5.4%).

The TEAEs that were reported by ≥10% of subjects are generally balanced between the 3 groups and the AEs occurring ≥10% in the combination arm are not unique to this treatment group and are also evident in the monotherapy groups. The toxicities in general are known risks associated with the mono-components such as GI toxicities, cardiac & thrombotic disorders, renal impairment, ototoxicity, hypersensitivity reactions, haematological toxicity and depression.

The most common TEAEs in the combination treatment group were ototoxicity, diarrhoea, fatigue, headache, arthralgia, back pain, decreased haemoglobin, nasopharyngitis and tinnitus. The only TEAE that varied by treatment more that 5% was ototoxicity (20.7% of subjects in the combination arm versus 13.7% in the placebo arm). The most common TEAEs reported as related to study drug in both groups were ear and labyrinth disorders, ototoxicity, and gastrointestinal disorders. Cardiac disorders were the only class of SAEs that occurred in more than 5% of subjects (5.3% of subjects in the combination treatment arm). Only 1 death occurred in the study, which was due to a traffic fatality.

In study CPP FAP-310, changes from baseline in haematology, chemistry, and urinalysis parameters were considered small and not clinically significant. Changes from baseline in vital sign parameters were small and not considered clinically significant. No subject experienced a treatment-emergent SAE or TEAE leading to study drug discontinuation related to an abnormal vital sign value.

Regarding the cardiac toxicity risk associated with NSAIDs and prolonged use, cardiac disorders namely arrhythmias occurred in low numbers in the combination arm (n=2) and there were no cerebrovascular events recorded in the combination arm. One retinal vein thrombotic evet occurred in the combination arm which was not considered an SAE. "Cardiovascular thrombotic events" has also been categorised as an important identified risk in the RMP. No cardiac disorders were recorded in the sulindac monotherapy arm. Three subjects, 1 in each arm respectively had abnormal, clinically significant non-serious ECG findings. None of the 3 needed to discontinue treatment for the abnormality. There were no cardiac disorders reported as an SAE across the 3 arms in the study. 1 CVA event was recorded under nervous system disorders in the eflornithine arm and 1 DVT in the sulindac arm, both as SAEs that were treatment related. A warning in section 4.4 of the SmPC was added to capture cardiac risks.

As with all NSAIDS, Flynpovi can lead to the onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to an increased incidence of cardiovascular events. Blood pressure would need to be monitored closely during the initiation of therapy with Flynpovi and throughout the course of therapy (see section 4.4 of the proposed SmPC).

For the immune system disorders, hypersensitivity and drug hypersensitivity occurred more frequently in the combination arm compared to the monotherapy. There also seems to be a higher rate of discontinuation due to these immune safety issues that occurred in the combination arm only with more rashes as an anaphylactic reaction TEAE. Rash is also listed as a treatment related TEAES reported by $\geq$ 5% of subjects (n=6, 10.7%) versus 0 in the two other groups. In evaluating the subjects that discontinued due to these events, three of the four subjects had a prior history of drug, chemical, and/or food sensitivities. In all four cases, the reactions occurred within the first 2 months of treatment. Language regarding hypersensitivity reactions and rash have been added to the proposed Product information. Hypersensitivity reactions are also listed in the RMP as an important identified risk.

Gastrointestinal toxicity is expected with sulindac due to its pharmacodynamics properties related to its NSAID profile, and in a lesser extent with eflornithine. Regarding GI ulceration and bleeding specifically: The numbers were similar between the combination arm and the NSAID only arm. TEAES that occurred in the combination arm only by PT were: haemorrhagic diarrhoea, duodenal ulcer, helicobacter gastric ulcer, erosive gastritis and peptic ulcer. These could potentially become more serous over time especially in patients taking other medication such as anti-platelets. While these risks are captured in the SmPC, listed as common ADRs and the RMP as an important identified risk, given that the intention of this medicine is for long term use, the applicant was requested to justify these common GI toxicities in this particular population further. The applicant presented data from the pivotal study in relation to upper GI disorders that resulted in drug interruptions or discontinuations for the combination arm which is reassuring however there is no supportive long-term data submitted. Erosive gastritis has been identified by the applicant as specific for the FDC with longer exposure.

Ototoxicity is a known adverse reaction associated to eflornithine with deafness as the main risk. Hence, audiometry measurements of subjects during the pivotal study were carried out. There were more patients in the combination arm that experienced hearing loss compared to the eflornithine monotherapy arm. The AESI hearing and vestibular disorders occurred more frequently in the 2 monotherapy arms compared to the FDC arm however when the PTs deafness and impaired hearing were reviewed separately, there were 3 cases each in both the FDC and sulindac arm and 1 case in the eflornithine arm. 1 subject in each monotherapy arm discontinued treatment due to ototoxicity which is not resolved. Overall these numbers are low despite ototoxicity being listed as a common ADR in the SmPC. Based on the available data, most of the patient hearing loss was reversible after treatment off which is a drawback since the combination sulindac/eflornithine is intended to be used chronically. In order to monitor this ADR the applicant proposed to recommend in the SmPC a serial audiograms annually and revise the warning about ototoxicity in section 4.4 of the SmPC.

In the pooled safety data from the pivotal study and the supportive PSCA study, ongoing TEAES at the end of study in the combination arm from the pivotal study are mainly hearing disorders n = 4, GI disorders n = 18, 2 unresolved liver disorders and the remaining occurring once in 1 PT e.g 1 weight increased. In contrast unresolved hearing disorders occur in higher numbers in the supportive PSCA study.

Evaluation of adverse events of special interest, 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. The seriousness of some of the eflornithine specific toxicities such as ototoxicity and bone marrow suppression need to be adequately characterised and communicated to patients and healthcare professionals.

The toxicities presented for both actives individually would be considered clinically significant however because there is no placebo only arm in the study, some of the AEs presented could have been due to their disease alone (+/- progression) or surgery related in particular the GI toxicities. The applicant states that *both drug substances are considered to have well-established medicinal use because of their respective systematic and documented clinical use in humans in settings other than FAP,* however this statement is not accurate because the authorised products are for different patient populations with a different benefit risk profile (facial hirsutism and African trypanosmiasis) neither are long-term or preventative treatments, the authorised doses, duration of treatment and formulations are different therefore the safety profile and assessments cannot be comparable.

The applicant submitted new safety data from placebo-controlled trials and that of the natural history of FAP. The applicant performed a literature search on trials performed with FAP patients containing a placebo arm or any natural history data comparing these to the non-placebo controlled pivotal data CPP-FAP 310.

The analysis is intended to address the lack of a placebo arm in CPP-FAP-310 which is acknowledged however does not completely resolve the issue given the limitations of such a literature review and across trial comparisons. However based on the assessments provided, it is agreed that some events in the GI tract, such as abdominal pain/discomfort, diarrhoea, nausea and rectal bleeding could be linked to the disease itself and not exacerbated by treatment with Flynpovi. This does not address the remaining uncertainties regarding ototoxicity, cardiovascular risk and GI effects such as ulcers and erosions in the long term which are known toxicities associated with both actives.

The safety data presented in study PSCA and in the updated analysis CAT-001 are supportive given the duration of the study and number of patients enrolled. However, several limitations for a direct comparison with the pivotal study (FAP-310) include: different dose for eflornithine (lower dose) and the option for a different eflornithine formulation (liquid formulation), different patient population (no patients had FAP) with more patients ≥65 years (30% approx.). Providing published literature from an external study as supportive safety data cannot be reliably assessed from a regulatory perspective given

the highlighted differences between the 2 studies. The focus of the safety assessment for the external study was based on the regulatory requested CAT-001 CSR.

In general, AE's occurred at a higher frequency in the combination arm in study FAP-310 compared to study CAT-001 (92.9% versus 91.5%) including treatment related AEs (67.9% versus 47%), AEs leading to discontinuation (16.1% versus 14.9%). In contrast, SAEs occurred at a higher frequency in study CAT-001 (22.9% versus 19.6%) but the applicant did not present data as to how many of these SAEs were considered treatment related. It would have been helpful if the applicant presented the results from the 2 studies in a table to compare. The applicant did not discuss the similarities and differences between the two studies in terms of the safety results adequately. Overall, the types of AEs by PTs were similar between the 2 studies. Cardiac disorders seemed to be more of concern in the PSCA study potentially due to a smaller sample size, younger patient population and the restrictions on cardiac risk factors in the inclusion criteria for study CPP FAP-310. When the higher risk subjects were excluded, the rates of cardiovascular events were comparable to the placebo group. The risk of serious cardiovascular complications associated with NSAIDs are now established in contrast to when the PSCA study started in 1998. While the numbers are small, there does not appear to be a trend for increased event rates with longer duration of treatment in either trial. However, the lifelong treatment exposure to this therapy in patients with FAP needs to be taken into account. Cardiovascular thrombotic events is an important identified risk in the RMP and should be assessed in the post marketing setting. Based on a summary of air conduction audiogram assessment, the applicant concluded that the estimated relative risk of clinically significant hearing loss, loss of 15 dB without recovery, in subjects treated with low doses of eflornithine + sulindac was 1.6 (95% CI, 0.96-2.62) relative to those taking placebo, adjusted for age and pretreatment thresholds at each frequency.

In addition, there was an early stopping decision by the Data Safety Monitoring Board (DSMB) for PSCA study which further limits the interpretation of the safety data: *The original PSCA Study was terminated early based on the recommendation of the Data Monitoring Committee (due to an interim analysis that demonstrated efficacy and concerns based on safety findings of other NSAID studies at the time). The trial was judged to be too small to generate additional insights regarding possible treatment adverse events, this included the risk of NSAID induced Major Adverse Cardiac Events (MACE).*

The integrated summary of safety (ISS) was intended to address if there were treatment related AEs or ADRs specific for the FDC product compared to the monotherapy arms or placebo as this analysis combined the safety from the CPP FAP-310 and PSCA trials, and to address the uncertainties and risks regarding long-term safety exposure.

Erosive gastritis was the only AE that occurred with combination treatment compared to monotherapy or placebo which is a known risk and ADR with NSAIDs and already captured in the labelling and RMP. Ototoxicity and deafness did not occur in more than 5% of the monotherapy arms but did in the placebo and combination treatment.

The SmPC lists the following ADRs as "common": deafness, ototoxicity, tinnitus and the following GI disorders: Gastritis erosive, rectal haemorrhage, gastroesophageal reflux disease, diarrhoea, vomiting, constipation, nausea, abdominal pain, abdominal distension, dyspepsia, haematochezia, flatulence. The applicant based the calculation of ADRs in the SmPC on two clinical studies, CPP FAP-310 and PSCA studies. The most frequent related adverse reactions reported included diarrhoea (8.6%) and ototoxicity (10.7%).

In view of the uncertainties in relation to genotoxicity and carcinogenicity, risk minimisation measures are required to further characterise the unknown long-term risk of malignancies. A warning on malignancies (including both solid & haematological cancers) was included in the SmPC and reflected in the RMP. Malignancies were proposed to be closely monitored in PSURs

As the FDC formulation is intended for long term use, there are major uncertainties with long term safety. The number of patients exposed to treatment decreased considerably during the course of the study and is clearly insufficient after 24 months of exposure to confirm adequate long-term exposure in a chemopreventative setting. Twenty nine (29) patients in the combination arm from the pivotal study is too low to conclude sufficient long term safety after 24 months of treatment in light of the significant efficacy issues discussed, the risks associated with both actives and the fact that this treatment is for long-term chemoprevention. While the number of patients receiving treatment after 24 months in the combination arm in the PSCA study is noted, (n= 137) this study is more supportive in nature and not considered enough to satisfactorily address the uncertainties regarding long term safety in patients with FAP. Across the 2 studies, there was only 1 patient receiving treatment >48 months and 12 (21.8%) patients in the pivotal study >36 months.

The applicant failed to submit adequate long-term safety data to support chronic use in the chemo-preventive setting. The safety profile and the potential serious safety concerns such as the high incidence of gastro-intestinal disorders, the risk of hearing loss due to eflornithine and the risk of cardiovascular/cerebrovascular side effects related to sulindac are significant considering it is intended for long term use in a young adult population.

Duration of treatment has not been specified. From a safety perspective, the duration of treatment required to reduce the incidence of cancer would be relevant in order to decide an acceptable benefit risk trade off and to manage the toxicities with appropriate long term follow up. The reduction of surgical morbidity by using chemoprevention has also not been discussed. It is important to also highlight the risk of interval cancers during treatment with sulindac has been reported and mentioned in clinical endoscopic guideline, as highlighted in the American Society for Gastrointestinal Endoscopy guideline on the role of endoscopy in familial adenomatous polyposis syndromes, published in 2020. *"There has been growing concern of a risk of interval cancer during therapy with sulindac because of a transformation of polyp morphology into a sessile nature, making them more difficult to visualise and resect with colonoscopy."*Yang J et al Gastrointest Endosc. 2020.

Two large rheumatology reviews were described which in the context of chemoprevention and long-term treatment in FAP is not considered applicable. While the two studies Giardello et al 2002 and Cruz Correa et al 2002 describe patients with FAP with a duration of dosing of up to 48 months and 98 months respectively, standard doses of sulindac did not prevent the development of adenomas in the first study and regrowth of polyps was observed soon after discontinuation of therapy, suggesting the need for continuous treatment. The number of patients in the prospective cohort study was too low n=12 to ascertain adequate long-term safety.

Clinical studies in various conditions have been presented where out of the 16 studies listed, only 1 is a FAP study (Lynch et al 2016) of short duration (6 months) with no long-term safety data provided. Some of the studies listed are not chemoprevention studies (Lipton et al 1989, Levin et al 1992) and a lot of the references provided are from the 1990s. No long-term follow-up safety data has been presented for any of the eflornithine studies and the applicant did not provide a discussion on the long-term safety data.

The applicant concludes that *long-term treatment with sulindac at doses from 150-400 mg/day was well tolerated in >50,000 subjects* however a reference has not been provided with this statement and it is assumed that this is in relation to the rheumatology population which should not be considered as pivotal long term safety data given that the duration of treatment for these conditions are shorter. No long-term safety exposure data for sulindac has been provided with this statement.

There is no relevant long-term follow up for any FAP study or patient registry available to alleviate the significant concerns and uncertainties regarding long-term safety for both active substances.

FAP is an incurable genetic condition, and polyps typically present during childhood and in adolescence. Chemoprevention is intended for long-term use. Patients with this condition undergo genetic counselling and also counselling for prophylactic surgery & stoma care including psychosexual health. Taking all this into account and the vulnerable age of the younger population, if authorised, patients would need to be fully informed of any risks associated with this medicine. For example, diarrhoea and abdominal pain caused by a medicine can impact on patients with a gastrointestinal disease especially if they also have a stoma in situ. The impact of alopecia and musculoskeletal disorders on a patient should not be underestimated especially in young adults. The patient should be able to make an informed decision of all risks, even rare ones that could be potentially serious.

The applicant noted that there is no information available in the vigilance databases on the FAP status of patients reporting adverse effects with either sulindac or eflornithine.

While overall the toxicities presented from the pivotal patient study did not demonstrate increased toxicities in the combination arm compared to the two monotherapy arms, the number of patients in each arm is low and neither active substances are approved for this condition which limits the safety assessment. Moreover, the long life treatment exposure to this therapy in patients with FAP need to be taken into account which has not been addressed sufficiently given that only 28 (16.4%) patients had a duration of exposure of more than 36 months across the 3 arms.

For the reasons outlined above, despite the updated RMP which proposes to capture safety in long term use as missing information and the Pharmacovigilance plan Post-Authorisation study on efficacy and safety study; the uncertainty regarding long-term safety remains.

### *Additional efficacy data needed in the context of a conditional MA*

In view of the negative benefit-risk, no conclusion can be reached at this stage on the proposed Specific Obligation to collect additional safety data in the context of a conditional MA.

## 2.6.2. Conclusions on the clinical safety

The lack of clinical utility and long-term safety data of each active component in this particular chemo-preventive setting has resulted in an overall negative safety assessment of the FDC in light of the potential serious risks related to each active substance. The uncertainty regarding long-term safety remains. In view of the fact that Flynpovi has failed to demonstrate unequivocal benefit for patients with FAP, the safety concerns are not considered acceptable.

## *2.7. Risk Management Plan*

## Safety Specification

#### *Summary of safety concerns*

The applicant identified the following safety concerns in the RMP:

**Part II: Module SVIII - Summary of the safety concerns**

**Table SVIII. 9: Summary of safety concerns**

| Summary of safety concerns | |
|---|---|
| Important identified risks | • GI disorders like GI bleeding, ulceration, perforation, ileus and small intestinal obstruction, diarrhoea, vomiting and abdominal pain<br>• Hypersensitivity reactions<br>• Ototoxicity including hearing loss on high doses (>2 g/m$^2$/day)<br>• Cardiovascular thrombotic events<br>• Bone marrow suppression<br>• Psychiatric disorders<br>• Renal impairment<br>• Pancreatitis acute<br>• Alopecia<br>• Musculoskeletal pain |
| Important potential risk | • Increased risk to foetus when exposed during pregnancy<br>• Hepatic impairment |
| Missing information | • Use in paediatric patients<br>• Use during lactation<br>• Safety in long term use<br>• Use in elderly patients with renal and/or hepatic impairment |

## Discussion on safety specification

In light of the AESIs and the known toxicities of these actives, the list of important identified and potential risks is now considered appropriate. The applicant added the following risks to the list of safety concerns in the updated version of the RMP dated 11th January 2021:

- long-term safety as missing information giving the proposed duration of treatment.
- renal impairment as an important identified risk in the safety specification given this is an established toxicity for NSAIDs specifically and this is a new indication proposed as long-term chemopreventative treatment.
- bone marrow suppression as an important identified risk.
- renal and/or hepatic impairment in elderly subjects as missing information specifically given the age profile of the pivotal study.

The applicant initially provided a list of risks not considered important to include as safety concerns. However given that chemoprevention is intended for long-term use, patients need to be fully informed of any risks associated with this medicine and these risks need to be fully characterised. For example, diarrhoea and abdominal pain can impact on patients especially if they also have a stoma and can be severe in nature. The impact of alopecia and musculoskeletal disorders on a patient should not be underestimated especially in young adults. These risks are now considered important and also captured in the SmPC.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated were also amended (acute pancreatitis and GI disorders like ileus and small intestinal obstruction).

Psychiatric disorders were reported as an AE in 17.5% of the patients in the sulindac monotherapy arm but was being omitted from the list of safety concerns in the RMP and no proposed warnings in the SmPC. The applicant was requested to capture the psychiatric disorders as a warning in the SmPC and the RMP safety concerns given that some were considered drug related, some were SAEs, there was premature discontinuation and some had not resolved.

## Conclusions on the safety specification

Having considered the data in the safety specification is adequate based on the assessment of the responses.

The rapporteur agrees that the safety concerns listed by the applicant are appropriate.

## Pharmacovigilance plan

### *Summary of additional PhV activities*

The applicant has proposed a category 3 study FAP-325: "A Randomized, Phase III Trial of the Efficacy and Safety of Eflornithine/Sulindac Compared to Sulindac in Delaying/Preventing the Need for Major Surgeries or Resection of Advanced Adenoma in the Lower Gastrointestinal Tract of Familial Adenomatous Polyposis (FAP) Subjects".

**Table 68: On-going and planned additional pharmacovigilance activities**

| **Study** *(study short name, and title)* **Status** *(planned/on-going)* | **Summary of objectives** | **Safety concerns addressed** | **Milestones** *(required by regulators)* | **Due dates** |
|---|---|---|---|---|
| **Category 1** - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation *(key to benefit risk)* | | | | |
| | | | | |
| **Category 2** – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances *(key to benefit risk)* | | | | |
| | | | | |
| **Category 3** - Required additional pharmacovigilance activities *(by the competent authority)* | | | | |
| A Randomized, Phase III Trial of the Efficacy and Safety of | The primary objective of FAP-325 is to demonstrate that the combination of eflornithine and sulindac | Long-term use, Gastrointestinal (such as bleeding, ulceration, and | Protocol preparation is ongoing. Milestone: To | Protocol preparation: Planned Milestones: |

| **Study** *(study short name, and title)* **Status** *(planned/on-going)* | **Summary of objectives** | **Safety concerns addressed** | **Milestones** *(required by regulators)* | **Due dates** |
|---|---|---|---|---|
| Eflornithine/Sulindac Compared to Sulindac in Delaying/Preventing the Need for Major Surgeries or Resection of Advanced Adenoma in the Lower Gastrointestinal Tract of Familial Adenomatous Polyposis (FAP) Subjects. Planned | treatment will delay disease progression in the lower GI tract compared to sulindac alone in adolescents and adults with genotypic FAP. Secondary objectives are to assess the changes in polyp burden compared to baseline, assess benefit in the intact colon, retained rectum, or pouch, and further delineate the safety profile of the combination therapy of eflornithine and sulindac. | perforation), ototoxicity (hearing loss, tinnitus), and cardiovascular/thrombotic (such as MI, CVA, DVT). | be planned. | To be planned |

The applicant has updated the RMP to Version 0.2 with the information of the Post-Authorisation follow on efficacy and safety study FAP-325 Part III.1, Part III.2, Part IV, Part V, Annex 2 and Annex 3.

The applicant proposes to submit the draft protocol later, however no the milestones have yet been proposed.

### Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan is not sufficient to identify and characterise the risks of the product.

From the current presentation of the proposed study, it is unclear if the study is suitable to characterise the safety concerns. The applicant should be requested to clarify how each safety concern will be characterised as part of additional pharmacovigilance activities and should specify the milestones of the FAP-325 study.

The applicant has updated the RMP to Version 0.2 with the information of the Post-Authorisation follow on efficacy and safety study FAP-325 Part III.1, Part III.2, Part IV, Part V, Annex 2 and Annex 3. FAP-310 study has been removed from RMP which is endorsed.

## Risk minimisation measures

### *Routine Risk Minimisation Measures*

The MAH proposed routine risk minimisation measures only.

**Table 69: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern**

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| GI disorders like GI bleeding, ulceration, and perforation, ileus | Routine risk minimisation measures:<br>• SmPC sections: 4.3, 4.4, 4.5, 4.8, and 4.9 | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| and small intestinal obstruction, diarrhoea, vomiting and abdominal pain | • PL sections: 2 and 4<br>• Prescription only medicine<br>Additional risk minimisation measures:<br>• No additional risk minimisation measures | • None proposed<br>Additional pharmacovigilance activities: Study title: A Randomized, Phase III Trial of the Efficacy and Safety of Eflornithine/Sulindac Compared to Sulindac in Delaying/Preventing the Need for Major Surgeries or Resection of Advanced Adenoma in the Lower Gastrointestinal Tract of Familial Adenomatous Polyposis (FAP) Subjects. Final study report: To be planned |
| Hypersensitivity reactions | Routine risk minimisation measures:<br>• SmPC sections: 4.3, 4.4 and 4.8<br>• PL sections: 2 and 4<br>• Prescription only medicine<br>Additional risk minimisation measures:<br>• No additional risk minimisation measures | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None proposed<br>Additional pharmacovigilance activities:<br>• None proposed |
| Ototoxicity including hearing loss on high doses (>2 g/m2/day) | Routine risk minimisation measures:<br>• SmPC sections: 4.3, 4.4 and 4.8<br>• PL sections: 2 and 4<br>• Recommendation to obtain serial audiograms annually when feasible is included in SmPC Section 4.4<br>• Prescription only medicine<br>Additional risk minimisation measures:<br>• No additional risk minimisation measures | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None proposed<br>Additional pharmacovigilance activities: A Randomized, Phase III Trial of the Efficacy and Safety of Eflornithine/Sulindac Compared to Sulindac in Delaying/Preventing the Need for Major Surgeries or Resection of Advanced Adenoma in the Lower Gastrointestinal Tract of Familial Adenomatous Polyposis (FAP) Subjects.<br>Final study report: To be planned |
| Cardiovascular thrombotic events | Routine risk minimisation measures:<br>• SmPC sections: 4.3, 4.4, 4.5 and 4.8<br>• PL sections: 2 and 4<br>• - Recommendation to monitor blood pressure closely during the initiation of therapy with Flynpovi CPP-1X/sul and | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None proposed<br>Additional pharmacovigilance activities: A Randomized, Phase III Trial of the Efficacy and Safety of |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| | throughout the course of therapy is included in SmPC section 4.4.<br>Prescription only medicine<br>Additional risk minimisation measures:<br>• No additional risk minimisation measures | Eflornithine/Sulindac Compared to Sulindac in Delaying/Preventing the Need for Major Surgeries or Resection of Advanced Adenoma in the Lower Gastrointestinal Tract of<br>Familial Adenomatous Polyposis (FAP) Subjects. Final study report: To be planned |
| Bone marrow suppression | Routine risk minimisation measures:<br>• SmPC sections: 4.4 and 4.8<br>• PL sections: 4<br>• SmPC section 4.4 mentions: - Complete pre-treatment blood counts (including platelets) should be assessed. - These values should be periodically monitored during the treatment with Flynpovi. - If a decrease in white blood cells, blood platelets, or significant bone-marrow suppression appears discontinuation or interruption of treatment with Flynpovi should be considered until values have returned to normal.<br>• Prescription only medicine<br>Additional risk minimisation measures: No additional risk minimisation measures | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None proposed<br>Additional pharmacovigilance activities:<br>• None proposed |
| Psychiatric disorders | Routine risk minimisation measures:<br>• SmPC sections: 4.4 and 4.8<br>• PL sections: 4<br>• SmPC section 4.4 mentions, 'Patients with history of depression should be monitored for signs of depression and referred for appropriate treatment, if necessary. Discontinuation of Flynpovi should be considered in severe cases.'<br>• Prescription only medicine<br>Additional risk minimisation measures:<br>No additional risk minimisation measures | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None proposed<br>Additional pharmacovigilance activities:<br>• None proposed |
| Renal impairment | Routine risk communication:<br>• SmPC sections: 4.2, 4.3, 4.4, 4.5, 4.8 and | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| | 5.2<br>• PL sections: 4<br>• Prescription only medicine<br>Additional risk minimisation measures:<br>No additional risk minimisation measures | • None proposed<br>Additional pharmacovigilance activities:<br>None proposed |
| Pancreatitis acute | Routine risk minimisation measures:<br>• SmPC sections: 4.8<br>• PL sections: 4 • Prescription only medicine<br>Additional risk minimisation measures: No additional risk minimisation measures | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None proposed<br>Additional pharmacovigilance activities:<br>• None proposed |
| Alopecia | Routine risk minimisation measures:<br>• SmPC sections: 4.4 and 4.8<br>• PL sections: 4<br>• Prescription only medicine Additional risk minimisation measures:<br>No additional risk minimisation measures | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None proposed<br>Additional pharmacovigilance activities:<br>• None proposed |
| Musculoskeletal pain | Routine risk minimisation measures:<br>• SmPC sections: 4.4 and 4.8<br>• PL sections: 4<br>• Prescription only medicine<br>Additional risk minimisation measures:<br>No additional risk minimisation measures | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None proposed<br>Additional pharmacovigilance activities:<br>• None proposed |
| Important potential risk | | |
| Increased risk to foetus when exposed during pregnancy | Routine risk minimisation measures:<br>• SmPC sections: 4.3, 4.6 and 5.3<br>• PL section: 2<br>• Prescription only medicine<br>Additional risk minimisation measures:<br>• No additional risk minimisation measures | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None proposed<br>Additional pharmacovigilance activities:<br>• None proposed |
| Hepatic impairment | Routine risk minimisation measures: | Routine pharmacovigilance activities beyond adverse reactions |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| | • SmPC sections: 4.2, 4.3, 4.4, 4.8 and 5.2<br>• PL sections: 2, 3 and 4<br>• SmPC section 4.4 mentions that Experience with Flynpovi in patients with mild and moderate hepatic impairment is limited, therefore such patients should be treated with caution and regularly monitored<br>• Prescription only medicine Additional risk minimisation measures:<br>• No additional risk minimisation measures | reporting and signal detection:<br>• None proposed<br>Additional pharmacovigilance activities:<br>• None proposed |
| Use in paediatric patients | Routine risk minimisation measures:<br>• SmPC section: 4.2<br>• PL section: 2<br>• Prescription only medicine<br>Additional risk minimisation measures:<br>• No additional risk minimisation measures | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None proposed<br>Additional pharmacovigilance activities:<br>• None proposed |
| Use during lactation | Routine risk minimisation measures:<br>• SmPC section: 4.6<br>• PL section: 2<br>• Prescription only medicine Additional risk minimisation measures:<br>• No additional risk minimisation measures | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None proposed<br>Additional pharmacovigilance activities:<br>• None proposed |
| Safety in long term use | Routine risk minimisation measures:<br>• SmPC section: 4.4<br>• Prescription only medicine<br>Additional risk minimisation measures:<br>• No additional risk minimisation measures | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None proposed<br>Additional pharmacovigilance activities:<br>A Randomized, Phase III Trial of the Efficacy and Safety of Eflornithine/Sulindac Compared to Sulindac in Delaying/Preventing the Need for Major Surgeries or Resection of Advanced Adenoma in the Lower Gastrointestinal Tract of Familial Adenomatous Polyposis |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| | | (FAP) Subjects.<br>Final study report: To be planned. |
| Use in elderly patients with renal and/or hepatic impairment | Routine risk minimisation measures:<br>• SmPC section: 4.2, 4.4 and 4.5<br>• PL section: 3<br>• Recommendation to monitor renal function of elderly patients is included in SmPC section 4.4.<br>• Recommendation of appropriate monitoring of potential gastrointestinal bleeding and of renal function in elderly patients with normal renal function or mild renal impairment who is taking Flynpovi in SmPC section 4.2.<br>• Recommendation to monitor patients taking methotrexate concomitantly with Flynpovi is included in SmPC section 4.5.<br>• Recommendation to monitor renal function of elderly patients concomitantly taking Flynpovi and diuretics is included in SmPC section 4.5.<br>• Prescription only medicine<br>Additional risk minimisation measures:<br>• No additional risk minimisation measures | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None proposed<br>Additional pharmacovigilance activities:<br>None proposed |

### *Summary of additional risk minimisation measures*

No additional RMMs have been proposed.

### *Overall conclusions on risk minimisation measures*

The PRAC Rapporteur, having considered the data submitted, was of the opinion that:

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The public summary of the RMP is acceptable

**PRAC Outcome**

The PRAC endorsed the PRAC Rapporteur's RMP assessment report and made additional comments. The PRAC noted that the current list of safety concerns is extensive and could be reduced in line with GVP V rev. 2 to focus on those safety concerns which require additional risk minimisation or further characterisation in a post-authorisation study taking into account the severity of the condition being treated. The PRAC agreed that the Phase III clinical trial FAP-325 as proposed by applicant generally lacks

enough details to assess the acceptability for inclusion in the Pharmacovigilance Plan. The applicant should clarify how it is planned to characterise the safety concerns with efficacy as its primary objective. Alternatively, the applicant should discuss how the safety concerns can be addressed in the post marketing setting by other means, including the option of undertaking a dedicated observational post-authorisation safety study. If the applicant would consider proposing another PASS; such discussion should include considerations on feasibility, and on the use of existing databases for data collection. The responses to the PRAC questions regarding the pharmacovigilance plan should consider any changes in the list of safety concerns which is pending final agreement by the CHMP.

### *Conclusion*

The CHMP and PRAC, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

## *2.8. Pharmacovigilance*

### *Pharmacovigilance system*

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

### *Periodic Safety Update Reports submission requirements*

Not applicable.

## *2.9. Product information*

In light of the negative recommendation, a satisfactory summary of product characteristics, labelling and package leaflet cannot be agreed at this stage.

### 2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found unacceptable as the COVID-19 restrictions cannot justify the proposal to submit the user consultation post approval.

The applicant will submit the results of a user consultation with target patient groups on the package leaflet that meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use* prior to placing the product on the market.

### 2.9.2. Additional monitoring

Not applicable.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

The proposed indication for Flynpovi (sulindac and eflornithine) is:

"Flynpovi is indicated as an adjunct to standard of care endoscopic surveillance for delaying the need for major surgery or resection of advanced adenoma in adult patients with familial adenomatous polyposis (FAP)."

FAP is a rare autosomal dominant disease caused by a defect in the adenomatous polyposis coli (APC) gene on chromosome 5q21. In patients with an inherited or spontaneous mutation genetic defect that causes FAP, the clinical course and hallmark of FAP is the development of hundreds of adenomatous polyps in the colon and rectum in teenagers and young adults, with an almost inevitable progression to colorectal cancer by the age of 35-40 years (Galiatsatos, 2006). The average age of cancer occurrence is 39 years (Burt, 1990). Therefore, most people with FAP undergo prophylactic surgery to remove the colon and in some cases, the rectum (Cetta, 2007; Mayo Clinic, 2009).

More than 90% of patients develop duodenal and ampullary adenomas. If not removed, these adenomas progress to malignancy in approximately 5% of cases.

A substantial number of FAP patients (10% to 20%) develop desmoids tumours located in the abdominal wall or intra-abdominally.

### 3.1.2. Available therapies and unmet medical need

Those patients that undergo proctocolectomy can still develop duodenal polyps that require subsequent management involving either additional surgical procedures or medical interventions. Adenomatous polyps that develop in the upper gastrointestinal tract, especially in the duodenum, if untreated, will progress to malignancy in approximately 5% of cases.

There are currently no available pharmacotherapies for management of patients with FAP. There is an unmet medical need in this patient population.

### 3.1.3. Main clinical studies

The application is based on a single pivotal clinical study CPP-FAP-310.

The Phase III pivotal study CPP-FAP-310 was a randomised, double-blind, study comparing the efficacy, safety, and pharmacokinetics of the CPP-1X (eflornithine hydrochloride [HCl])/sulindac combination vs. CPP-1X and sulindac as single agents, in subjects with FAP.

## *3.2. Favourable effects*

No statistically significant difference between the combination treatment group and either single-agent treatment group for time from the date of randomisation to the date of the first occurrence of any FAP-related event was observed in the prespecified analyses by disease stratum group (pre-colectomy, duodenal polyposis, and rectal/pouch polyposis).

The applicant claimed an effect on time to first FAP related event in patients with intact lower GI anatomy based on a post-hoc exploratory analysis in which the applicant restricted the primary endpoint definition by censoring SS progression and excision of polyps >/=10mm or HGD. However, due to methodological weaknesses of such analyses, such claims cannot be considered established.

## *3.3. Uncertainties and limitations about favourable effects*

Demonstration of efficacy is based on one pivotal study only, which failed to meet its primary endpoint and did not show any difference between combination CPP-1X + sulindac versus either single agent monotherapy arm alone in delaying time to first FAP-related event.

The comparator arms are both investigational, and efficacy has not been demonstrated for their effect in FAP. A placebo-controlled study would have been more informative.

The protocol and statistical analysis plan underwent multiple revisions, including revision of the main secondary endpoints, with addition of a new measurement of investigator-assessed change which has not been validated.

Notwithstanding the aforementioned weaknesses in terms of design of the study and results, the lack of independent review of endoscopies and the short duration of follow-up add additional uncertainties in terms of robustness and clinical relevance of the study results.

## *3.4. Unfavourable effects*

The TEAEs that were reported by ≥10% of subjects are generally balanced between the 3 groups and the AEs occurring ≥10% in the combination arm are not unique to this treatment group and are also evident in the monotherapy groups. The toxicities in general are known risks associated with the mono-components such as GI toxicities, cardiac & thrombotic disorders, renal impairment, ototoxicity, hypersensitivity reactions, haematological toxicity and depression.

Regarding the cardiac toxicity risk associated with NSAIDs and prolonged use, cardiac disorders namely arrhythmias occurred in low numbers in the combination arm (n=3). One retinal vein thrombotic event occurred in the combination arm which was not considered an SAE.

For the immune system disorders, hypersensitivity and drug hypersensitivity occurred more frequently in the combination arm compared to the monotherapy. There also seems to be a higher rate of discontinuation due to these immune safety issues that occurred in the combination arm only with more rashes as an anaphylactic reaction TEAE. Rash is also listed as a treatment related TEAES reported by ≥ 5% of subjects (n=6, 10.7%) versus 0 in the two other groups.

Only serious GI events occurred during the pivotal study CPP-FAP-310.

## *3.5. Uncertainties and limitations about unfavourable effects*

GI toxicities occurred in over 70% of patients in the combination arm and were considered the most common treatment related TEAE. However, because there is no placebo only arm in the study, some of the AEs presented could have been due to their disease alone (+/- progression) or surgery related in particular the GI toxicities.

The toxicities associated with chronic NSAID use, while widely known in a different clinical setting is a limitation in terms of concluding a positive benefit risk profile.

Generally, the safety profile with systemic use of eflornithine is not well established given that the clinical utility of this active substance in the EU is a topical cream for hirsutism. The reversibility of the ototoxicity is an uncertainty based on the data submitted.

Unresolved AEs that are due to chemoprevention eg ototoxicity affects the benefit risk trade off for the patient when the management is endoscopic & surgical management alone without therapeutic intervention.

No long-term safety exposure data is available for either mono-component as neither are authorised chemo-preventive products.

The submitted dossier is not considered sufficient to support an adequate non-clinical safety assessment of this fixed-dose combination of eflornithine and sulindac in the absence of *in vivo* genotoxicity studies for both components.

## *3.6. Effects Table*

**Table 70: Effects Table for Flynpovi as an adjunct to standard of care for treatment of adult patients with familial adenomatous polyposis (FAP). 2nd April 2020.**

| Effect | Short Description | Unit | Treatment<br>FDC<br>n=56 | Control<br>Sulindac<br>n= 58<br>CPP-1X<br>n= 57 | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| Time to first FAP related event | Composite endpoint incorporating FAP related events of disease progression, excisional intervention, need for surgery, cancer and death | Subjects with any FAP-related event<br><br>n (%)<br>HR<br>95% CI<br>P-value | FDC<br>18 (32.1) | Sulindac<br>22 (37.9)<br>0.71<br>(0.4,1.3)<br>0.2898<br><br>CPP1X<br>23 (40.4)<br>0.66<br>(0.36,1.24)<br>0.2001 | Statistical significance not met<br><br>Very slight numerical trend only | CSR<br><br>SCE |
| **Unfavourable Effects** | | | | | | |
| Gr ≥3 TEAE | Number of patients with Grade ≥3 TEAE | N (%) | FDC<br>12 (21.4) | Sulindac<br>12 (21.1)<br><br>CPP-1X<br>17 (30.4) | | |
| AEs leading to discontinuation | Number of patients with AEs leading to discontinuation | N (%) | FDC<br>9 (16.1) | Sulindac<br>6 (10.5)<br><br>CPP-1X<br>5 (8.9) | | |

| Effect | Short Description | Unit | Treatment<br>FDC<br>n=56 | Control<br>Sulindac<br>n= 58<br>CPP-1X<br>n= 57 | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| Cardiovascular, Embolic, Thrombotic TEAEs | AESI | No. of events (%) | FDC<br>1 (1.8) | Sulindac<br>1 (1.8)<br>CPP-1X<br>2 (3.6) | One subject in each treatment group experienced an embolic or thrombotic TEAE. Retinal vein thrombosis in the combination arm was not considered an SAE. No cardiac disorders reported as an SAE across the 3 arms. | Pivotal study FAP-310 |
| Ototoxicity | AESI | No. of events (%) | FDC<br>3 (5.4) | Sulindac<br>3 (5.3)<br>CPP-1X<br>1 (1.8) | Reversibility in some of these subjects need to be clarified. | Pivotal study FAP-310 |
| GI perf, ulceration, haemorrhage of obstruction | AESI | No. of events (%) | FDC<br>20 (35.7) | Sulindac<br>23 (40.4)<br>CPP-1X<br>15 (26.8) | Long term effects of these toxicities need to be justified further. | Pivotal study FAP-310 |
| Immune System disorder hypersensitivity | AE | No. of events (%) | FDC<br>4 (7.2) | Sulindac<br>1 (1.8)<br>CPP-1X<br>0 | Hypersensitivity lead to treatment discontinuation in the FDC compared to 0 in the monotherapy arms | Pivotal study FAP-310 |
| Anaphylactic reaction (erythema, pruritus, rash, pruritic rash, urticaria) | AESI | No. of events (%) | FDC<br>15 (26.8) | Sulindac<br>6 (10.5)<br>CPP-1X<br>3 (5.4) | More cases in the FDC arm | Pivotal study FAP-310 |

Abbreviations: CVA=cerebrovascular accident, X=subject, AESI = adverse event of special interest

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

In view of the results and many methodological weaknesses of the analyses presented, what benefit Flynpovi can add above current standard of care of regular endoscopic screening with intervention as required, is unclear. Flynpovi has not been shown to delay or avoid the need for further surgery, as was prospectively planned. Furthermore, no investigation of whether Flynpovi could potentially delay the time between endoscopic surveillance has been explored. Both of these aims could be considered meaningful for patients with FAP but neither have been demonstrated. For physicians treating patients with FAP, it is not considered that Flynpovi would offer any advantage over current standard of care, but would risk potential non-negligible adverse events of a long-term treatment.

Whilst overall the toxicities presented from the pivotal study did not demonstrate increased events in the combination arm compared to the two monotherapy arms, the number of patients in each arm is low and neither active substances are approved for this condition which limits the safety assessment. The duration of exposure after 36 months is very limited.

Notwithstanding that benefits have not been established, the lifelong treatment exposure to this therapy in patients with FAP needs to be taken into account while assessing the benefit risk profile and the uncertainty regarding the long-term safety concerns which has not been alleviated as no long term exposure data for either active substances have been submitted by the applicant and both mono-components and more specifically eflornithine are not well established in the treatment of patients with FAP.

## 3.7.2. Balance of benefits and risks

In the setting of a long-term treatment with two known actives with significant toxicity profiles, the clinical benefit of the combination Flynpovi cannot be considered established.

Notwithstanding that benefits have not been established, taking into consideration the age of the population and the clinically significant toxicities (gastrointestinal, ototoxicity, cardiovascular/thrombotic, anaphylactic reaction, hematopoietic cytopoenia, depression) that are associated with both active substances and the identified risks, the long-term exposure to this FDC is an additional uncertainty and a major limitation. The toxicities and risks presented for this chemoprevention in a genetic disease could negatively affect a patient's quality of life if there is no acceptable trade off in terms of efficacy, which has not been established with Flynpovi.

In summary, the single pivotal CPP-FAP 310 study failed to demonstrate a benefit of eflornithine + sulindac in patients with FAP. The exploratory post-hoc analyses cannot establish efficacy. The benefit risk balance cannot therefore be considered positive.

## 3.7.3. Additional considerations on the benefit-risk balance

### *Conditional marketing authorisation*

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a seriously debilitating and potentially life-threatening disease. In addition, the product is designated as an orphan medicinal product.

The CHMP considers that the product cannot be recommended for a conditional marketing authorisation as:

- The benefit-risk balance is negative (as discussed above);
- The applicant's ability to provide comprehensive data post-approval to confirm the benefit-risk balance in the approved indication:

  The applicant plans to generate comprehensive safety and efficacy data with a blinded, randomised trial comparing fixed dose combination eflornithine plus sulindac versus sulindac plus eflornithine placebo. The reduction in the need for and the delay of the time for major surgeries or the development of pre-cancerous advanced adenomas in the lower GI will be measured as efficacy outcomes. The treatment duration will be 3 years. The study design (choice of sulindac as a comparator, absence of a placebo arm) is not justified. No clear start/due date are provided, it is only estimated that the trial could be completed in approximately 6 years (2-3 years for accrual and 3 years of treatment time). Because FAP is a rare disease, patient enrolment into a clinical trial could be challenging. The applicant stated that Flynpovi will not be available to patients in many parts in

Europe for 2-3 years and that this time-lag will facilitate the enrolment of patients in the specific obligation. The applicant plans to include international sites and the international clinical community has committed to collaborate in future trials. However, the 2 to 3 years delay announced before product availability in Europe seems to be overestimated. Inclusion of subjects of age ≥16 years is being considered to facilitate accrual of patients with intact colon and to meet an unmet need in this lower age group. To conclude the CHMP questioned whether the applicant will be able to provide comprehensive data taking into account the uncertainties and the limitations in the proposed confirmatory study proposed by the applicant as specific obligation.

- It is recognised that there is an unmet medical need in the revised claimed indication. Considering that the efficacy of Flynpovi is not demonstrated, the applicant could not demonstrate that it would fulfil an unmet medical need.
- Taking into account that efficacy is not demonstrated, the considerable uncertainties regarding long-term safety, the uncertainties and the limitations of the proposed specific obligation, the applicant could not demonstrate that the benefit to public health of the medicinal product's immediate availability on the market outweighs the risks due to need for further data.

### *3.8. Conclusions*

The overall B/R of Flynpovi is negative.

# 4. Recommendations

### *Outcome*

Based on the CHMP review of data on quality, safety and efficacy for Flynpovi as an adjunct to standard of care for treatment of adults patients with familial adenomatous polyposis (FAP) who have an intact colon, rectum, or ileo-anal pouch, the CHMP considers by consensus that the safety and efficacy of the above mentioned medicinal product is not sufficiently demonstrated and, therefore recommends the refusal of the granting of the conditional marketing authorisation for the above mentioned medicinal product. The CHMP considers that:

- The submitted dossier is not considered sufficient to support an adequate non-clinical safety assessment of this fixed-dose combination of eflornithine and sulindac in the absence of the required genotoxicity studies for both components.
- The single pivotal CPP-FAP 310 study failed to demonstrate a statistically significant effect of eflornithine + sulindac in delaying the time to first occurrence of any FAP-related event. The exploratory post-hoc analyses are considered hypothesis-generating and cannot support a marketing authorisation without further confirmatory studies.
- The uncertainty regarding long-term safety remains a concern and because of the failed pivotal study, the benefit does not outweigh the risks.
- Taking into account the negative benefit-risk of Flynpovi, the unmet medical needs would not be considered fulfilled and the benefit to public health of the medicinal product's immediate availability on the market would not outweigh the risks inherent to the fact that additional data are still required, therefore a conditional marketing authorisation cannot be considered.

The CHMP is of the opinion that pursuant to Article 12 of Regulation (EC) No 726/2004, the efficacy and safety of the above-mentioned medicinal product is not properly or sufficiently demonstrated. Therefore,

the CHMP has recommended the refusal of the granting of the conditional marketing authorisation for Flynpovi.