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ORIGINAL CONTRIBUTION

# Combination of Sulindac and Eflornithine Delays the Need for Lower Gastrointestinal Surgery in FAP Patients: Post-Hoc Analysis of a Randomized Clinical Trial

**Short running head:** Eflornithine/sulindac utility in FAP LGI

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**ABSTRACT**

***BACKGROUND:*** Colectomy and proctocolectomy are the initial standard of care for patients with familial adenomatous polyposis. Pharmacotherapy to prevent progression of polyposis and surgeries in the lower gastrointestinal tract would be beneficial to patients with this disease.

***OBJECTIVE:*** This analysis aimed to evaluate the impact of eflornithine-sulindac combination versus monotherapy in delaying time to disease progression in the lower gastrointestinal tract of patients with familial adenomatous polyposis.

***DESIGN:*** This is a post-hoc analysis of a randomized phase 3 trial.

***SETTING:*** Twenty-one hospitals in 7 countries treating patients with familial adenomatous polyposis.

***PATIENTS:*** Adults with familial adenomatous polyposis were randomized 1:1:1 into 3 arms.

***INTERVENTIONS:*** Patients received either eflornithine (750 mg), sulindac (150 mg), or both once daily for up to 48 months.

***MAIN OUTCOME MEASURES:*** Efficacy was evaluated as time from randomization to predefined primary disease progression endpoints.

***RESULTS:*** Results are reported for the study population excluding patients who had undergone permanent ileostomies (n = 158). Disease progression was observed in 2/54 (3.7%), 9/53 (17.0%), and 10/51 (19.6%) patients with at least partial lower gastrointestinal tract in the combination, sulindac, and eflornithine arms, respectively, corresponding to risk reductions of 80% ($p = 0.02$) and 83% ($p = 0.01$) between combination and sulindac or eflornithine, respectively. When endoscopic excision of

adenomas ≥10 mm in size were censored, the need for major surgery was observed in 0/54, 7/53 (13.2%), and 8/51 (15.7%) patients in the combination, sulindac, and eflornithine arms, respectively, corresponding to risk reductions approaching 100% between combination and sulindac ($p = 0.005$) or combination and eflornithine ($p = 0.003$).

***LIMITATIONS:*** This was a post-hoc analysis, the sample size was small, and there were fewer than expected events.

***CONCLUSIONS:*** Eflornithine-sulindac combination therapy was superior to either drug alone in delaying or preventing the need for lower gastrointestinal tract surgery in patients with familial adenomatous polyposis. See **Video Abstract** at http://links.lww.com/DCR/B658 .

***REGISTRATION*:** NCT01483144; EudraCT2012-000427-41

**LA COMBINACIÓN DE SULINDAC Y EFLORNITINA RETRASA LA NECESIDAD DE CIRUGÍA DEL TUBO DIGESTIVO BAJO EN PACIENTES CON PAF: ANÁLISIS POST-HOC DE UN ENSAYO CLÍNICO ALEATORIZADO**

***ANTECEDENTES:*** La colectomía y la proctocolectomía son el estándar inicial de atención para los pacientes con poliposis adenomatosa familiar. La farmacoterapia para prevenir la progresión de la poliposis y las cirugías en el tracto gastrointestinal inferior sería beneficiosa para los pacientes con esta enfermedad.

***OBJETIVO:*** Este análisis tuvo como objetivo evaluar el impacto de la combinación de eflornitina-sulindac versus la monoterapia en el retraso del tiempo hasta la progresión de

la enfermedad en el tracto gastrointestinal inferior de pacientes con poliposis adenomatosa familiar.

***DISEÑO:*** Este es un análisis post-hoc de un ensayo de fase 3 aleatorizado.

***ENTORNO CLINICO***: Veintiún hospitales en 7 países que tratan a pacientes con poliposis adenomatosa familiar.

***PACIENTES:*** Adultos con poliposis adenomatosa familiar fueron aleatorizados 1: 1: 1 en 3 brazos.

***INTERVENCIONES:*** Los pacientes recibieron eflornitina (750 mg), sulindac (150 mg) o ambos una vez al día durante un máximo de 48 meses.

***PRINCIPALES MEDIDAS DE VALORACION:*** La eficacia se evaluó como el tiempo desde la aleatorización hasta los criterios de valoración primarios predefinidos de progresión de la enfermedad.

***RESULTADOS:*** Los resultados se informan para la población de estudio excluyendo a los pacientes que se habían sometido a ileostomías permanentes (n = 158). Se observó progresión de la enfermedad en 2/54 (3,7%), 9/53 (17,0%) y 10/51 (19,6%) pacientes con al menos tracto gastrointestinal inferior parcial en los brazos de combinación, sulindac y eflornitina, respectivamente, correspondientes al riesgo de reducciones del 80% (p = 0,02) y del 83% (p = 0,01) entre la combinación y el sulindaco o la eflornitina, respectivamente. Cuando se censuró la escisión endoscópica de adenomas ≥10 mm de tamaño, se observó la necesidad de cirugía mayor en 0/54, 7/53 (13,2%) y 8/51 (15,7%) pacientes en la combinación, sulindac y eflornitina, respectivamente, correspondientes a reducciones de riesgo cercanas al 100% entre combinación y sulindac (p = 0,005) o combinación y eflornitina (p = 0,003).

***LIMITACIONES:*** Este fue un análisis post-hoc, el tamaño de la muestra fue pequeño y hubo menos eventos de los esperados.

***CONCLUSIONES:*** La terapia de combinación de eflornitina-sulindac fue superior a cualquier fármaco solo para retrasar o prevenir la necesidad de cirugía del tracto gastrointestinal inferior en pacientes con poliposis adenomatosa familiar. Consulte **Video Resumen** en http://links.lww.com/DCR/B658 . *(Traducción—Dr. Adrian Ortega)*

***KEY WORDS***: Efficacy; Eflornithine-sulindac combination; Familial adenomatous polyposis; Lower gastrointestinal tract;

## INTRODUCTION

Familial adenomatous polyposis (FAP) is most commonly caused by germline mutations in the adenomatous polyposis coli (*APC*) gene and characterized initially by progressive development of hundreds to thousands of adenomatous polyps in the colon and rectum.[1–3] Regular colonoscopy surveillance is recommended from diagnosis until either colectomy with ileorectal anastomosis (IRA) or proctocolectomy with ileostomy or ileal pouch-anal anastomosis (IPAA) is indicated for prophylactic treatment of progressive polyposis, advanced disease, inability to adequately survey the colon to prevent cancer, or cancer.[4–6] In addition to the spectrum of potential complications associated with surgery, neither IRA nor IPAA are a cure for FAP.[6–10] Furthermore, they do not eliminate the need for continued surveillance,[6–10] or additional surgery.[10–13] The surgical procedures negatively affect patients' quality of life (QoL).[10,12] Pharmacotherapy would enhance FAP disease management by delaying or avoid the occurrence of advanced colorectal adenomas, the need for complex polypectomy, and/or the need for life-altering lower gastrointestinal (LGI) surgery.

Sulindac, a non-steroidal anti-inflammatory drug (NSAID) that influences polyamine and cyclooxygenase metabolism,[14] has been used off-label for treatment of FAP with variable short-term success.[15–17] In a placebo-controlled study, treatment of patients with sporadic colorectal adenomas with a combination of sulindac and eflornithine reduced mucosal polyamines in the LGI tract and reduced risk of metachronous advanced adenoma at 3 years.[18] In patients with FAP, a combination of eflornithine with celecoxib demonstrated a 40% reduction in global polyp burden.[19] In several other studies, treatment with sulindac alone delayed polyposis in the LGI tract among patients with FAP.[20] Thus, it is

reasonable to expect that the primary effect of combination therapy with sulindac and eflornithine would be observed among patients with at least a partially intact LGI tract. The CPP FAP-310 trial (NCT01483144), which compared the efficacy and safety of combination therapy with sulindac and eflornithine versus monotherapies, showed no statistical difference between the treatment arms using a composite primary endpoint that included prevention of both upper and lower GI surgery for up to 4 years.[21,22] Based on the available evidence, including the efficacy of this combination in preventing sporadic adenomas in the colorectum,[18] this combination therapy could be beneficial to FAP patients with intact colon, retained rectum, or ileal pouch (LGI subpopulation). In this paper, we report our post-hoc analysis undertaken to evaluate the efficacy of combination therapy versus monotherapies focusing on delays in the need for life-altering LGI surgery due to adenoma progression in the LGI subpopulation.

## MATERIALS AND METHODS

### Study Design, Setting, and Participants

Details of the study design of this multinational, multicenter, double-blind, randomized trial, approved by all local institutional review boards, conducted at 21 centers in 7 countries have been published previously.[21] Briefly, adult patients with FAP, a germline pathogenic variant of the *APC* gene, and any of the following on baseline endoscopy: (1) intact colon – moderate adenoma burden (100–1000 polyps) being considered for prophylactic surgery; (2) retained rectum or ileal pouch ≥3 years since IRA or IPAA surgery with International Society for Gastrointestinal Hereditary Tumours (InSiGHT) stage 1, 2, or 3 polyposis[23] and excision of any polyp ≥5 mm at baseline; or (3) duodenum with Spigelman Stage III or IV polyposis or Stage III or IV that has been

down-staged to Spigelman Stage I or II within the last 6 months were included. The stratification was based on disease state. Patients with major personal cardiovascular risk factors or using hearing aids were excluded from the study.[24] Patients were randomized 1:1:1 to receive either 750 mg eflornithine, or 150 mg sulindac, or both orally once daily for up to 48 months. In the monotherapy arms, patients received a placebo pill to mimic the medication they were not receiving. Patients underwent upper GI and LGI endoscopy every 6 months to assess disease status; endoscopies were conducted by endoscopists experienced in FAP and blinded to the treatment. This post-hoc analysis was undertaken on patients with a partial or fully intact lower gastrointestinal tract (an anatomical grouping) and excluded 13 patients who had a permanent ileostomy and focused on the treatment effect on time to first LGI disease progression event.

**Endpoints**

For the current analysis, the primary efficacy endpoint, a composite measure of time to first disease progression in the LGI tract, was defined as the endoscopist's recommendation for the (1) need for colectomy or proctocolectomy; (2) need for proctectomy or pouch excision, (3) endoscopic excision of any polyp ≥10 mm in size in the rectum or pouch, and/or (4) diagnosis of high-grade dysplasia or cancer in the rectum or pouch. The "need for surgery" was based on recommendations by experienced FAP endoscopists who had received standardization and calibration training. In the absence of cancer, patients were not required to undergo surgery as part of the trial and could choose if and when they would have their operation. Patients were monitored for adverse events (AEs) and serious AEs (SAEs) and are reported on all patients who received at least 1 dose of study drug in accordance with National Cancer Institute's Common Terminology

Criteria for Adverse Events (CTCAE) Version 4.0.[25] Treatment-emergent AEs (TEAEs) were defined as any AE occurring after administration of the first dose of study drug and through 30 days after the last dose of study drug.

**Statistical analysis**

The composite primary endpoint, time to any polyposis site prespecified disease progression event in the combination treatment compared with each drug alone, was determined for the intent-to-treat (ITT) population using a 2-sided, stratified, log-rank test using the score method ($\alpha = 0.05$) and reported graphically as Kaplan-Meier survival curves.[22] Hazard ratio (HR) of probability of having a disease progression event was derived from the Cox proportional analysis, and the score method was used to derive the 95% confidence interval (CI) for the HR for each comparison. Patients with UGI disease progression endpoints without a concurrent LGI disease progression endpoint were censored at the time when the UGI event was reported. An additional analysis also censored patients with endoscopic resection of large adenomas, to separate polyp removal from the more clinically significant disease progression with need for surgery.

**RESULTS**

**Patients**

The LGI subpopulation (N = 158) included 38 patients with intact colons, 53 whose status was post-colectomy with IRA, and 67 whose status was post-proctocolectomy with IPAA. One patient who was randomized to receive eflornithine but was not treated was included in the ITT population for efficacy analysis, but not included in the safety population. Baseline patient demographics and disease characteristics were generally comparable across the 3 treatment arms, combination (N = 54), sulindac (N = 53), and

eflornithine (N = 51) (Table 1); the proportion of patients who had undergone an IPAA was greater in the combination arm than in the monotherapy arms. More patients with retained rectum or pouch in the combination arm had advanced polyposis burden than in the monotherapy arms.

**Efficacy**

Disease progression in the LGI tract occurred in 2/54 (3.7%), 9/53 (17.0%), and 10/51 (19.6%) patients in the combination, sulindac, and eflornithine arms, respectively, corresponding to risk reductions for LGI interventions of 80% (hazard ratio [HR] = 0.20; 95% confidence interval [CI]: 0.05, 0.8; $p$ =0.020) and 83% (HR = 0.17; 95% CI: 0.04, 0.69; $p$ = 0.010) between combination and sulindac or eflornithine, respectively, in a time to event analysis (Table 2; Figure 1).

When patients who underwent endoscopic excision of polyps ≥10 mm in size were censored (n = 6, 2 in each treatment arm), none of the patients in the combination arm progressed to a need for LGI surgery for up to 48 months compared with 7 (13.2%) and 8 (15.7%) patients in the sulindac and eflornithine arms, respectively (Table 2; Figure 2). These data corresponded to risk reductions for need for LGI surgery approaching 100% between combination and either monotherapy with HR = 0.00 (95% CI: 0.00, 0.48; $p$ = 0.005) for combination versus sulindac and HR = 0.00 (95% CI: 0.00, 0.44; $p$ = 0.003) for combination versus eflornithine.

In the intact colon group (n = 38), none of the patients in the combination arm (n = 13) had disease progression indicating the need for a colectomy or proctocolectomy for up to 48 months compared with 4 (30.8%) and 3 (25.0%) patients in the sulindac (n = 13) and eflornithine (n = 12) arms, respectively (Table 2; Figure 3). These data corresponded to

risk reductions for need for LGI surgery approaching 100% between combination and either monotherapy with HR = 0.00 (95% CI: 0.00, 1.08; $p = 0.06$) for combination versus sulindac and HR = 0.00 (95% CI: 0.00, 1.38; $p = 0.10$) for combination versus eflornithine.

In the group of patients that had an IRA or IPAA (n = 120), 2/41 (4.9%) patients in the combination arm showed disease progression during the study compared with 5/40 (12.5%) and 7/39 (17.9%) patients in the sulindac and eflornithine arms, respectively (Table 2). These data corresponded to risk reductions for need for LGI surgery and excision of polyps ≥10 mm in size with or without high-grade dysplasia of 64% (HR = 0.36 (95% CI: 0.08, 1.60); $p = 0.20$) between combination and sulindac treatment, and 76% (HR = 0.24 (95% CI: 0.56, 1.01; $p = 0.05$) between combination and eflornithine treatment. When patients in this group who only underwent excision of polyps ≥10 mm in size with or without high-grade dysplasia (n = 6, 2 in each treatment arm) were censored, no patient in the combination arm had the need for LGI surgery for up to 48 months compared with 3 (7.5%) and 5 (12.8%) in the sulindac and eflornithine arms, respectively (Table 2). These data corresponded to risk reductions for LGI interventions approaching 100% between combination and either monotherapy with HR = 0.00 (95% CI: 0.00, 1.17; $p = 0.07$) for combination versus sulindac and HR = 0.00 (95% CI: 0.00, 0.72; $p = 0.02$) for combination versus eflornithine.

When post-colectomy patients who had severe disease in the retained rectum or pouch (InSIGHT stages 2 and 3) at baseline were evaluated for disease progression events (need for surgery or removal of a polyp ≥10 mm in size with or without high-grade dysplasia),

only 1/23 (4.3%) patient in the combination arm had disease progression compared with 5/23 (21.7%) patients in the sulindac arm and 6/18 (33.3%) in the eflornithine arm.

**Safety**

Safety data for the whole study population have been reported previously in detail.[22] The safety profiles were comparable between the treatment arms in the LGI safety population (Table 3). Most TEAEs were mild to moderate in severity and resolved with minimal intervention. Overall, nausea (18.5%), headache (14.6%), vomiting (13.4%), abdominal pain (12.1%), diarrhea (12.1%), nasopharyngitis (11.5%), fatigue (10.8%), and upper respiratory tract infection (10.8%) were the most common TEAEs reported. Serious TEAEs for small intestinal obstruction were reported by 2 patients each in the combination (3.7%) and sulindac (3.8%) arms. Nine (16.7%), 6 (11.3%), and 4 (7.8%) patients in the combination, sulindac, and eflornithine arms, respectively, discontinued treatment due to AEs.

**DISCUSSION**

The main goals of treatment for patients with FAP are to prevent cancer and maintain patient QoL.[7,8,26] This can be accomplished by minimizing increases in adenoma number and size, and the development of advanced adenomas.[7,8,26] Such a strategy will provide opportunities to delay or avoid life-altering surgery and associated reduced QoL.[27] Prevention of advanced adenomas has been recognized as an appropriate endpoint in pharmacotherapy trials.[22,28,29]

Our analysis of the data in patients with at least a partially intact LGI tract in the CPP FAP-310 trial demonstrated that they responded very well to combination treatment with sulindac and eflornithine exhibiting ≥80% reduction in risk for disease progression

compared with either drug alone. This benefit with combination therapy was observed despite the much lower than anticipated number of patients exhibiting disease progression in the monotherapy arms. The low numbers of patients with confirmed disease progression precluded calculating the median or mean time to disease progression for all 3 treatment arms of the LGI subpopulation. These data are consistent with previous reports showing that single agent sulindac has limited long-term efficacy in reducing polyposis in the LGI tract,[30,31] and that a combination of eflornithine with NSAIDs reduces global polyp burden.[19]

Under normal conditions, the pool of polyamines is tightly controlled through regulation of synthesis, catabolism, and transport mechanisms mediated through ornithine decarboxylase (ODC) and spermidine/spermine N1-acetyltransferase 1.[32] In patients with FAP, inactivation of the *APC* gene causes dysregulation of ODC, increasing its activity and polyamine levels in the colonic mucosa.[32–34] It is known that colonic bacteria are important for sulindac metabolism and generating active metabolites.[35] In clinical settings, studies have demonstrated efficacy of sulindac in delaying LGI polyposis in FAP patients with intact colons and those who have undergone colectomy with IRA.[20] In addition to inhibiting cyclooxygenase and reducing inflammation, sulindac also induces polyamine export and catabolism thereby decreasing the concentration of polyamines and inhibiting tumor development.[36] In an animal model for FAP, treatment with eflornithine reduced polyposis in the small intestine.[37] Since eflornithine and sulindac independently reduce polyamine levels through inhibition of *de novo* synthesis and induction of catabolism, respectively,[34] they could act additively or synergistically when administered together. In a controlled study involving 375 patients with resected sporadic adenoma at

baseline, treatment with a combination of low-dose eflornithine and low-dose sulindac reduced the risk of subsequent metachronous adenomas in the LGI tract by 70% overall, advanced adenomas by 92%, and multiple adenomas by 95%.[18] Both these data and ours support the concept that a combination of eflornithine and sulindac is effective in preventing polyposis progression in the LGI tract.

While endoscopic excisions of adenomas ≥10 mm in size, one of the disease progression events in our trial, is a measure of disease severity, it is not as clinically significant as the need for LGI surgery. To evaluate the impact of these endoscopic excisions, we censored patients who developed adenomas ≥10 mm during the study. We postulated that fewer patients on combination therapy than on monotherapy would exhibit disease progression indicating the need for LGI surgery. Although the number of patients with disease progression were much lower than expected for both sulindac and eflornithine, the absence of any patients with disease progression with need for LGI surgery in the combination arm resulted in a theoretical risk reduction of 100% for patients receiving combination therapy compared with either drug alone, suggesting that combination therapy may be particularly effective in preventing or delaying disease progression requiring LGI surgical interventions. Thus, early detection and initiation of combination therapy may have the greatest benefit to patients by preserving normal anatomy and function and also maintaining their QoL.

The major limitation of this analysis, common to all trials in rare diseases, was the small number of patients enrolled despite this study being one of the largest trials on pharmacotherapy in patients with FAP. Potentially, this can be addressed by an additional trial focused on patients with at least a partially intact LGI tract (colon, retained rectum,

or ileal pouch) evaluating disease progression in the LGI as a primary endpoint. Since most FAP patients require colectomy by their late teens or 20s, it is likely that such a trial will have to include a younger patient population than in the current study in order to include a sufficient number of pre-colectomy patients.[8,38,39] Another limitation was the much lower observed disease progression event rates in the monotherapy arms compared with the expected 70% based on our literature review.[29] Although the combination arm resulted in the expected disease progression event rate of ~30%, the event rates in the monotherapy arms were much lower than expected; consequently, we lacked power to estimate the median time-to-event (disease progression) even in these treatment arms. It is rare for cancers to occur within 10 years among patients whose polyps have been eliminated by sulindac monotherapy.[31,40–42] However, these data may not apply to combination therapy. Nevertheless, an abundance of caution necessitates continued close surveillance and longer term follow up of patients on chemoprevention.

The opportunity to delay prophylactic colectomy/proctocolectomy for adolescents and young adults could be beneficial for several reasons. Although prophylactic colectomy remains the standard of care for patients with severe colorectal polyposis that is not amenable to endoscopic control, this can be associated with morbidity, mortality, and lower QoL.[6–10] Regardless of the type of surgery, the risk for desmoid tumors (the second leading cause of FAP-related deaths) and serious morbidity increases with each surgery in FAP patients, particularly those with certain *APC* mutations.[43,44] Both IRA and IPAA also alter patients' bowel habits, resulting in more frequent bowel movements (on average 4 and 6 per day after IRA and IPAA, respectively) and a higher risk of noctunal fecal incontinence.[7,8,26,27] In recent years, laparoscopic methods have improved outcomes

with quicker postoperative recovery and reduced impact on reproductive potential. Nevertheless, all colectomies and proctocolectomies are life-altering surgeries with significant comorbidities that often results in reduced QoL.[7,8,26,27] Controlling rectal and pouch polyposis through pharmacotherapy would potentially maintain normal bowel function, avoiding the mucosal scarring associated with polypectomy, the need for any type of stoma, and minimizing the risk for desmoid disease. In the near future, pharmacotherapy with a combination of eflornithine and sulindac will not obviate the need for regular endoscopic examinations. Even if such therapy does not replace the need for colectomy, it could offer patients with FAP, especially those who have an intact colon, the opportunity to meaningfully control or delay polyposis progression, giving them more options with regard to the timing of surgery and the type of operation that is best for them based on their personal preferences. To our knowledge, this is the first report of sustained delay for up to 48 months to disease progression using a pharmacotherapy regimen to treat patients with FAP.

**CONCLUSIONS**

In conclusion, our data demonstrate a clinically important benefit of combination therapy with eflornithine and sulindac over monotherapy in delaying disease progression in the LGI tract (intact colon/rectum/pouch) in patients with FAP. There were no internal invasive cancers. The combination treatment was well tolerated.

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## FIGURE LEGENDS

**FIGURE 1.** Kaplan-Meier plot on time to first LGI disease progression in the LGI population.

**FIGURE 2.** Kaplan-Meier plot on time to first LGI disease progression in the LGI population censored for patients with excisions of ≥10 mm polyps.

**FIGURE 3.** Kaplan-Meier plot on time to first LGI disease progression in patients with an intact colon.

**TABLE 1.** Baseline patient demographics and disease characteristics (mean (SD), unless otherwise stated) of the LGI population

| Characteristic | Combination (N=54) | Sulindac (N=53) | Eflornithine (N=51) |
|---|---|---|---|
| Male, n (%) | 33 (61.1) | 35 (66.0) | 25 (49.0) |
| Age, y | 37.4 (13.4) | 37.1 (13.4) | 38.1 (14.5) |
| Race, n (%) | | | |
| White | 46 (85.2) | 46 (86.8) | 48 (94.1) |
| Black | 6 (11.1) | 3 (5.7) | 1 (2.0) |
| Other | 2 (3.7) | 4 (7.5) | 2 (3.9) |
| BMI, $kg/m^2$ | 27.2 (6.0) | 27.2 (5.6) | 28.2 (6.3) |
| Surgical status, n (%) | | | |
| Intact colon | 13 (24.1) | 13 (24.5) | 12 (23.5) |
| InSIGHT Stage | | | |
| Stage 0/1 | 11 | 10 | 10 |
| Stage 2/3 | 2 | 3 | 1 |
| Stage 4 | 0 | 0 | 1 |
| Polyp number | | | |
| 1-100 | 2 | 4 | 2 |
| 101-1000 | 11 | 9 | 9 |

| | | | |
|---|---|---|---|
| >1000 | 0 | 0 | 1 |
| Polyp ≥10 mm | 5 | 10 | 6 |
| Colectomy with IRA | 13 (24.1) | 19 (35.8) | 21 (41.2) |
| InSIGHT Stage | | | |
| Stage 0/1 | 3 | 6 | 11 |
| Stage 2/3 | 10 | 13 | 9 |
| Stage 4 | 0 | 0 | 1 |
| Polyp number | | | |
| 0-10 | 3 | 3 | 4 |
| 11-25 | 0 | 4 | 8 |
| >25 | 10 | 12 | 9 |
| Polyp ≥10 mm | 10 | 7 | 10 |
| Proctocolectomy with IPAA | 28 (51.9) | 21 (39.6) | 18 (35.3) |
| InSIGHT Stage | | | |
| Stage 0/1 | 15 | 11 | 9 |
| Stage 2/3 | 13 | 10 | 9 |
| Stage 4 | 0 | 0 | 0 |
| Polyp number | | | |
| 0-10 | 10 | 7 | 9 |

| | | | |
|---|---|---|---|
| 11-25 | 7 | 6 | 3 |
| >25 | 11 | 8 | 6 |
| Polyp ≥10 mm | 8 | 9 | 5 |

BMI, body-mass index; InSIGHT, International Society for Gastrointestinal Hereditary Tumours; IPAA, ileal pouch anal anastomosis; IRA, ileorectal anastomosis; LGI, lower gastrointestinal tract

**TABLE 2.** Analysis LGI disease progression in LGI study population*

| Patients/Statistic | Combination | Sulindac | Eflornithine |
|---|---|---|---|
| LGI ITT population | 54 (100) | 53 (100) | 51 (100) |
| FAP-related LGI disease progression | 2 (3.7) | 9 (17.0) | 10 (19.6) |
| Need for LGI surgery | 0 (0) | 6 (11.3)** | 8 (15.7) |
| Excision of ≥10 mm adenomas ± HGD | 2 (3.7) | 3 (3.8) | 2 (3.9) |
| Intact colon subgroup | 13 (100) | 13 (100) | 12 (100) |
| FAP-related LGI disease progression | 0 | 4 (30.8) | 3 (25.0) |
| | | | |
| Need for LGI surgery | 0 (0) | 4 (30.8) | 3 (25.0)) |
| Combined IRA and IPAA subgroup | 41 | 40 | 39 |
| FAP-related LGI disease progression | 2 (4.9) | 5 (12.5) | 7 (17.9) |
| Need for LGI surgery | 0 (0) | 2 (5.0) | 5 (12.8) |
| Excision of ≥10 mm adenomas ± HGD | 2 (4.9) | 3 (7.5) | 2 (5.1) |
| IRA subgroup | 13 (100) | 19 (100) | 21 (100) |
| FAP-related LGI disease progression | 1 (7.7) | 3 (15.8) | 4 (19.9) |

| | | | |
|---|---|---|---|
| Need for LGI surgery | 0 (0) | 1 (5.3)** | 3 (14.3) |
| Excision of ≥10 mm adenomas ± HGD | 1 (7.7) | 2 (10.5) | 1 (4.8) |
| IPAA subgroup | 28 (100) | 21 (100) | 18 (100) |
| FAP-related LGI disease progression | 1 (3.6) | 2 (9.5) | 3 (16.7) |
| Need for LGI surgery | 0 (0) | 1 (4.8) | 2 (11.1) |
| Excision of ≥10 mm adenomas ± HGD | 1 (3.6) | 1 (4.8) | 1 (5.6) |

*All data are given as number of patients with percentage in parentheses

**1 patient had need for surgery and excision of ≥10 mm adenoma ± HGDCI

FAP, familial adenomatous polyposis; HGD, high-grade dysplasia; IPAA, ileal pouch anal anastomosis; IRA, ileorectal anastomosis; ITT, intent-to-treat; LGI, lower gastrointestinal tract

[a]Hazard ratio of probability of having a disease progression event was derived from the Cox proportional hazards model; score method was used to calculate 95% CI for hazard ratio for each comparison between the combination treatment and single drug alone

**TABLE 3**. Summary of adverse events reported by ≥10% of patients in any treatment arm in accordance with National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.[25]

| Characteristic | Eflornithine/sulindac (N = 54)* | Sulindac (N = 53)* | Eflornithine (N = 50)* |
|---|---|---|---|
| Number of patients reporting TEAEs | 50 (92.6) | 47 (88.7) | 43 (86.0) |
| Number of patients reporting TEAEs ≥Grade 3 | 13 (24.1) | 10 (18.9) | 14 (28.0) |
| Number of patients reporting TESAEs | 11 (20.4) | 8 (15.1) | 11 (22.0) |
| Number of patients discontinuing due to a TEAE | 9 (16.7) | 6 (11.3) | 4 (7.8) |
| Death | 0 | 0 | 0 |
| Number of patients reporting following AEs | | | |
| Nausea | 12 (22.2) | 10 (18.9) | 7 (14.0) |
| Headache | 8 (14.8) | 11 (20.8)) | 4 (8.0) |
| Abdominal pain | 8 (14.8) | 7 (13.2) | 4 (8.0) |
| Upper respiratory tract infection | 8 (14.8) | 7 (13.2) | 2 (4.0) |
| Diarrhea | 7 (13.0) | 5 (9.4) | 7 (14.0) |
| Rectal hemorrhage | 7 (13.0) | 7 (13.2) | 2 (4.0) |

| | | | |
|---|---|---|---|
| Gastroenteritis | 7 (13.0) | 5 (9.4 | 2 (4.0) |
| Upper abdominal pain | 7 (13.0) | 1 ( 1.9) | 4 ( 8.0) |
| Vomiting | 6 (11.1) | 2 (3.8) | 5 (10.0) |
| Nasopharyngitis | 6 (11.1) | 4 (7.5) | 8 (16.0) |
| Hematochezia | 6 (11.1) | 2 (3.8) | 5 (10.0) |
| Influenza-like illness | 5 (9.3) | 3 (5.7) | 5 (10.0) |
| Back pain | 5 (9.3) | 2 (3.8) | 5 (10.0) |
| Oropharyngeal pain | 5 (9.3) | 1 (1.9) | 5 (10.0) |
| Fatigue | 4 (7.4) | 7 (13.2) | 6 (12.0) |
| Sinusitis | 4 (7.4) | 1 (1.9) | 5 (10.0) |
| Cough | 3 (5.6) | 4 (7.5) | 5 (10.0) |
| Dyspepsia | 2 (3.7) | 5 (9.4) | 5 (10.0) |
| Tinnitus | 2 (3.7) | 6 (11.3) | 1 (2.0) |

*All data are given as number of patients with percentage in parentheses

AE, adverse event; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event

Figure 1

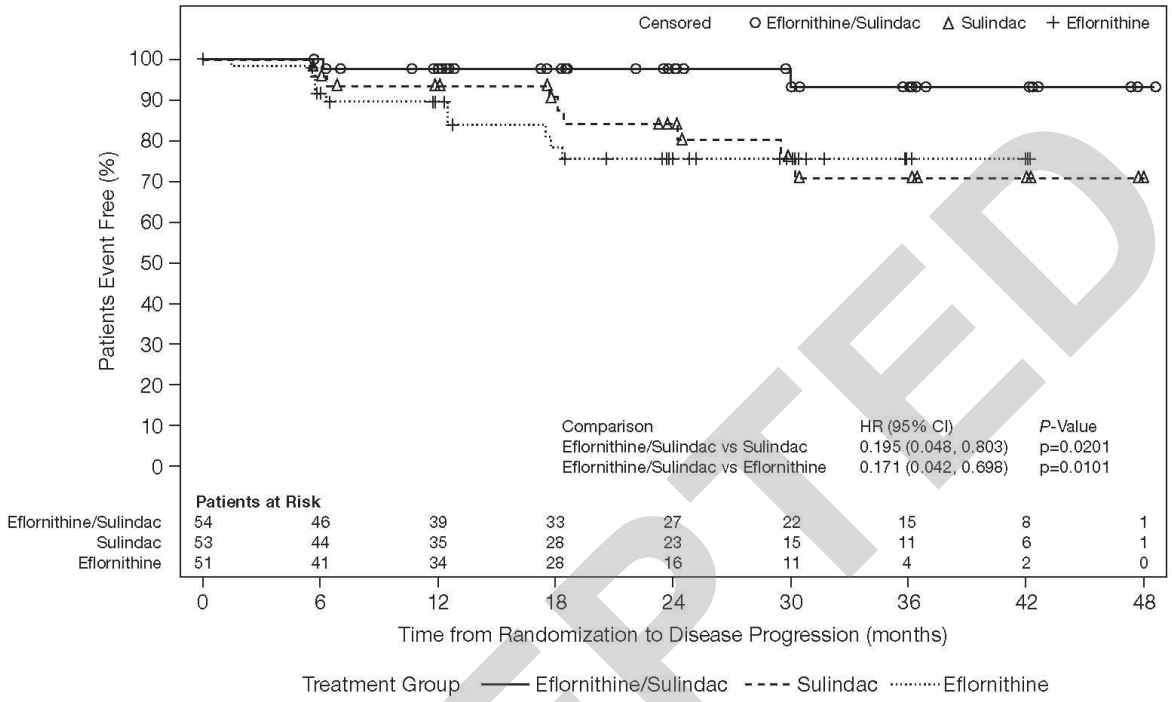

Figure 2

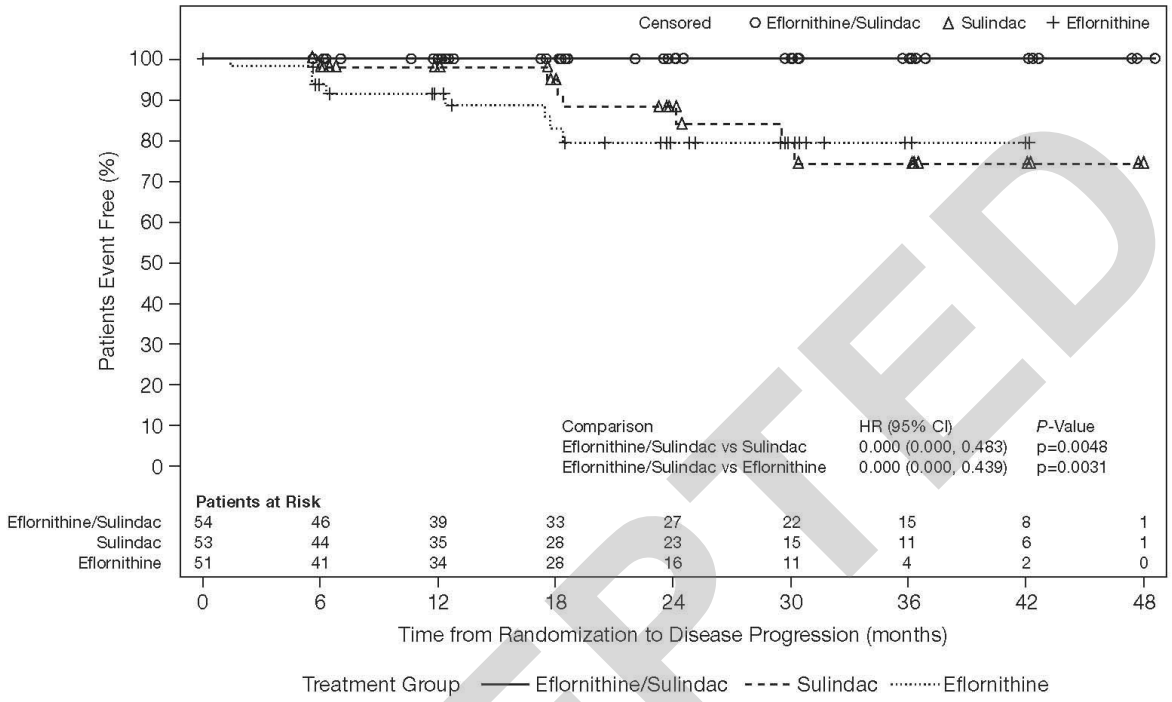

Figure 3