ORIGINAL ARTICLE

Eflornithine plus Sulindac for Prevention of Progression in Familial Adenomatous Polyposis

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ABSTRACT

BACKGROUND

The efficacy and safety of combination therapy with eflornithine and sulindac, as compared with either drug alone, in delaying disease progression in patients with familial adenomatous polyposis are unknown.

METHODS

We evaluated the efficacy and safety of the combination of eflornithine and sulindac, as compared with either drug alone, in adults with familial adenomatous polyposis. The patients were stratified on the basis of anatomical site with the highest polyp burden and surgical status; the strata were precolectomy (shortest projected time to disease progression), rectal or ileal pouch polyposis after colectomy (longest projected time), and duodenal polyposis (intermediate projected time). The patients were then randomly assigned in a 1:1:1 ratio to receive 750 mg of eflornithine, 150 mg of sulindac, or both once daily for up to 48 months. The primary end point, assessed in a time-to-event analysis, was disease progression, defined as a composite of major surgery, endoscopic excision of advanced adenomas, diagnosis of high-grade dysplasia in the rectum or pouch, or progression of duodenal disease.

RESULTS

A total of 171 patients underwent randomization. Disease progression occurred in 18 of 56 patients (32%) in the eflornithine–sulindac group, 22 of 58 (38%) in the sulindac group, and 23 of 57 (40%) in the eflornithine group, with a hazard ratio of 0.71 (95% confidence interval [CI], 0.39 to 1.32) for eflornithine–sulindac as compared with sulindac (P=0.29) and 0.66 (95% CI, 0.36 to 1.23) for eflornithine–sulindac as compared with eflornithine. Among 37 precolectomy patients, the corresponding values in the treatment groups were 2 of 12 patients (17%), 6 of 13 (46%), and 5 of 12 (42%) (hazard ratios, 0.30 [95% CI, 0.07 to 1.32] and 0.20 [95% CI, 0.03 to 1.32]); among 34 patients with rectal or ileal pouch polyposis, the values were 4 of 11 patients (36%), 2 of 11 (18%), and 5 of 12 (42%) (hazard ratios, 2.03 [95% CI, 0.43 to 9.62] and 0.84 [95% CI, 0.24 to 2.90]); and among 100 patients with duodenal polyposis, the values were 12 of 33 patients (36%), 14 of 34 (41%), and 13 of 33 (39%) (hazard ratios, 0.72 [95% CI, 0.34 to 1.52] and 0.76 [95% CI, 0.35 to 1.64]). Adverse and serious adverse events were similar across the treatment groups.

CONCLUSIONS

In this trial involving patients with familial adenomatous polyposis, the incidence of disease progression was not significantly lower with the combination of eflornithine and sulindac than with either drug alone. (Funded by Cancer Prevention Pharmaceuticals; ClinicalTrials.gov number, NCT01483144; EudraCT number, 2012-000427-41.)

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Familial adenomatous polyposis is a rare, autosomal dominant, hereditary colorectal cancer syndrome that is most commonly caused by pathogenic germline variants in the adenomatous polyposis coli (*APC*) gene.[1-3] In its classic presentation, familial adenomatous polyposis is characterized by progressive development of hundreds to thousands of adenomatous polyps in the lower gastrointestinal tract, mainly in the colon and rectum, and is associated with up to a 100% lifetime risk of colorectal cancer if left untreated.[1,4] Upper gastrointestinal tract polyposis develops in the duodenum in more than 80% of patients with familial adenomatous polyposis, and duodenal or periampullary cancer occurs in 5 to 12% of these patients.[5,6] Proctocolectomy is the standard of care for the management of colorectal polyposis,[7] and among patients who had undergone an initial colectomy and ileorectal anastomosis, proctectomy with ileal pouch–anal anastomosis resection is performed in up to 30% because of progressive polyposis or cancer.[8-10] However, colectomy and proctocolectomy are associated with complications, including diarrhea, fecal incontinence, and adverse effects on sexual function, fertility, and health-related quality of life.[11-15] In the majority of patients with familial adenomatous polyposis, management of duodenal adenomas is necessary in addition to management of the initial colorectal polyposis[16]; mesenteric desmoid tumors may also develop in these patients.[15,17] Because surgical and endoscopic treatment do not completely eliminate the potential for future polyps or extraintestinal neoplasms, there is an unmet medical need for the identification and use of pharmacologic agents to delay major endoscopic excisional or surgical interventions.

Cyclooxygenase (COX) and ornithine decarboxylase (ODC) are enzymes that are normally negatively regulated by *APC* and are overexpressed in tumor tissue.[18,19] ODC, the rate-limiting enzyme in the polyamine pathway, and mucosal polyamine levels are also elevated in polyps in patients with familial adenomatous polyposis.[20] Trials of pharmacologic prevention with nonsteroidal antiinflammatory drugs (NSAIDs) to prevent or delay the progression of polyps in patients with familial adenomatous polyposis or to prevent the development of advanced adenomas in patients with sporadic polyps have yielded limited benefit.[21-27] NSAIDs increase polyamine catabolism and export through COX-dependent and COX-independent mechanisms and complement inhibitors of polyamine synthesis to lower tissue polyamine levels.[28]

A 3-year randomized, placebo-controlled trial of a combination of eflornithine, an irreversible inhibitor of ODC, plus low-dose sulindac for the prevention of sporadic adenomas showed that the risk of subsequent advanced colorectal adenomas was more than 90% lower with combination therapy than with placebo.[25] Celecoxib, a COX-2 inhibitor, at a high dosage was briefly approved for the treatment of familial adenomatous polyposis on the basis of a 28% reduction from baseline in the mean number of colorectal polyps in patients in a 6-month trial.[29] Although familial adenomatous polyposis has been removed from the list of approved uses of celecoxib, treatment with celecoxib and eflornithine enhanced regression of total polyp burden, as determined by video-based global assessment.[24] These clinical data provide proof of concept that polyamine inhibition combined with NSAIDs as a potential approach for pharmacologic prevention could delay progression of familial adenomatous polyposis. The most important and unmet clinical needs that could be addressed would be to delay or avoid surgery or advanced endoscopic resection and to prevent the progression of polyposis. We conducted a randomized, double-blind, phase 3 trial to evaluate the efficacy and safety of a new combination therapy with eflornithine and sulindac, as compared with either drug alone, and used a time-to-event analysis with a composite efficacy end point to determine the delay in disease progression or major endoscopic or surgical procedures in patients with familial adenomatous polyposis.

METHODS

TRIAL DESIGN

The trial was designed by the sponsor, Cancer Prevention Pharmaceuticals, under the direction of the last author and in consultation with the academic authors. The first draft of the manuscript was written by the first four authors and the last author with the assistance of a medical writer, in accordance with Good Publication Practice guidelines, employed by rareLife solutions (funded in part by Cancer Prevention Pharmaceuticals and Mallinckrodt Pharmaceuticals). The authors were required to give the sponsor 30

days to review any submissions or publications to ensure the accuracy of the data, compliance with regulatory agency requirements, and nondisclosure of intellectual property. The authors vouch for the accuracy and completeness of the data and analyses and for fidelity of the trial to the protocol, available with the full text of this article at NEJM.org.

The details of the protocol, which was approved by the local institutional review board at each site of this multinational, multicenter trial, have been published previously.[17] The data and safety monitoring committee received confidential reports on a periodic basis and was responsible for decisions regarding possible termination of the trial for either futility or safety reasons.

PATIENTS

Adults 18 years of age or older who had clinical familial adenomatous polyposis and pathogenic variants of *APC* were eligible for inclusion in this trial if they had any of the following endoscopic findings at baseline: an intact colon with moderate adenoma burden (100 to 1000 polyps) for which prophylactic surgery was under consideration; a retained rectum or ileal pouch (≥3 years since ileorectal anastomosis or ileal pouch–anal anastomosis surgery) with stage 1, 2, or 3 polyposis according to the International Society for Gastrointestinal Hereditary Tumours (InSiGHT) classification (stages range from 0 to 4, with higher stages indicating greater severity of disease) (Table S1 in the Supplementary Appendix, available at NEJM.org) and excision of any polyp with a diameter greater than 1 cm at the first trial-related endoscopy[30]; or a duodenum with current stage 3 or 4 polyposis according to the modified Spigelman duodenal scoring system and classification or polyposis that had been down-staged to Spigelman stage 1 or 2 within the 6-month period before screening (stages range from 0 to 4, with higher stages indicating a higher 10-year cumulative risk of duodenal cancer and a higher frequency of esophagogastroduodenoscopy) (Table S2).[31] Patients at high risk for cardiovascular disease[32] or who had clinically significant hearing loss for which a hearing aid was used were not eligible. In order to minimize imbalance among the treatment groups, the patients were stratified before randomization on the basis of the anatomical site with the highest polyp burden and surgical status; the three strata were precolectomy (shortest projected time), rectal or ileal pouch polyposis after colectomy (longest projected time), or duodenal polyposis (intermediate projected time).

RANDOMIZATION

The patients were randomly assigned in a 1:1:1 ratio to receive 750 mg of eflornithine, 150 mg of sulindac, or both once daily for up to 48 months; treatment was administered orally as four tablets. The patients in the two monotherapy groups received a placebo matching the other drug in the combination. Patients underwent upper and lower gastrointestinal endoscopy every 6 months to assess disease status.

END POINTS

The primary efficacy end point, assessed in a time-to-event analysis, was disease progression, defined as a composite of major surgery (colectomy, proctocolectomy, duodenal polyp or ampullary excisions, duodenectomy, Whipple procedure, or pouch or retained rectum resection), excision of any polyp that was at least 1 cm in diameter in the retained rectum or pouch, diagnosis of high-grade dysplasia in the rectum or pouch, or duodenal disease progression of at least 1 stage in the Spigelman classification. A secondary efficacy end point, also assessed in a time-to-event analysis, was disease progression among the patients in each of the three surgical subgroups.

Patients were monitored for adverse events and serious adverse events, which were reported in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[33] An adverse event that occurred during the treatment period was defined as any adverse event that occurred after the administration of the first dose of a trial drug through 30 days after the last dose was administered. A treatment-related adverse event was defined as any adverse event that was considered to be possibly, probably, or definitely related to trial drug, as determined by the investigator and reviewed by the medical monitor, both of whom were unaware of the treatment-group assignments. Laboratory results were monitored to detect any safety signals.

STATISTICAL ANALYSIS

The sample-size calculation was based on an expected overall incidence of familial adenomatous

polyposis–related events of 30% with combination therapy and 70% with monotherapy over 2 years, as determined primarily from published literature on the effects of eflornithine or NSAIDs on polyposis.[34] We calculated that we would need to assign 50 to 55 patients to each treatment group for the trial to have 85% power to detect a significant difference between eflornithine–sulindac therapy and monotherapy with either drug, with a 40 percentage-point lower incidence of familial adenomatous polyposis–related events in the eflornithine–sulindac group. The time-to-event analysis of the primary composite end point of disease progression in the eflornithine–sulindac group, as compared with either drug alone, was performed in the intention-to-treat population with the use of a two-sided stratified log-rank test at an alpha level of 0.05, and the results were reported graphically as Kaplan–Meier curves. In the analysis of the primary composite end point, data from the patients who were lost to follow-up were censored at the time their status was last known. Because the median time to the first event could not be estimated owing to the small number of events, the mean time to the first event was reported as an alternative quantitative measure. The mean time was estimated as the area under the curve (the integral of the survival function). The Proc Lifetest program in SAS statistical software, version 9.4 (SAS Institute), was used to estimate the mean by summing the rectangular areas under the estimated step function used with the Kaplan–Meier, Breslow, and Fleming–Harrington estimators. The mean survival time was underestimated when the maximum event time was less than the maximum censored time in each treatment group.

Continuous data were evaluated with the use of an analysis of covariance model with treatment as the main effect and the baseline value and surgical subgroup as covariates. Categorical data were analyzed with the use of chi-square tests and the Cochran–Mantel–Haenszel test to control for subgroup. Ordered categorical data were analyzed with the use of Kruskal–Wallis nonparametric tests. Safety was assessed without inferential statistics in all patients who received at least one dose of a trial drug. To control type I error in the primary end-point analysis, a sequential testing approach was used, with the primary comparison being between the eflornithine–sulindac group and the sulindac group. If the primary comparison was significant at the 0.05 level, the test proceeded to the next comparison between the eflornithine–sulindac group and the eflornithine group.

RESULTS

PATIENTS

A total of 250 patients underwent screening, and 171 underwent randomization — 56 to the eflornithine–sulindac group, 58 to the sulindac group, and 57 to the eflornithine group (Fig. 1). The baseline demographic and clinical characteristics of the patients were similar across the treatment groups (Table 1).

PRIMARY EFFICACY ANALYSIS

The primary composite end point of disease progression occurred in 18 of 56 patients (32%) in the eflornithine–sulindac group, 22 of 58 patients (38%) in the sulindac group, and 23 of 57 patients (40%) in the eflornithine group (Table 2). Kaplan–Meier estimated mean times to the first event of disease progression in the intention-to-treat population were 32.3 months (95% confidence interval [CI], 31.8 to 32.8) in the eflornithine–sulindac group, 23.6 months (95% CI, 23.2 to 23.9) in the sulindac group, and 21.8 months (95% CI, 21.4 to 22.2) in the eflornithine group; the hazard ratio in the eflornithine–sulindac group, as compared with the sulindac group, was 0.71 (95% CI, 0.39 to 1.32; $P=0.29$), and the hazard ratio in the eflornithine–sulindac group, as compared with the eflornithine group, was 0.66 (95% CI, 0.36 to 1.24) (Fig. 2).

Upper or lower gastrointestinal cancer did not develop in any patient during the trial. Twelve patients had progression of lower gastrointestinal polyposis (two polypectomies were performed in the eflornithine–sulindac group, two colectomies, one proctectomy, and four polypectomies were performed in the sulindac group, and one pouch resection and two polypectomies were performed in the eflornithine group). A total of 14 patients with progression of duodenal polyposis underwent duodenal surgery (5 in the eflornithine–sulindac group, 6 in the sulindac group, and 3 in the eflornithine group) (Table S1). Disease progression in the duodenum involved progression in Spigelman stage in 30 patients and duodenal endoscopic excisional intervention in 19 patients. Only 8 of the 30 patients with

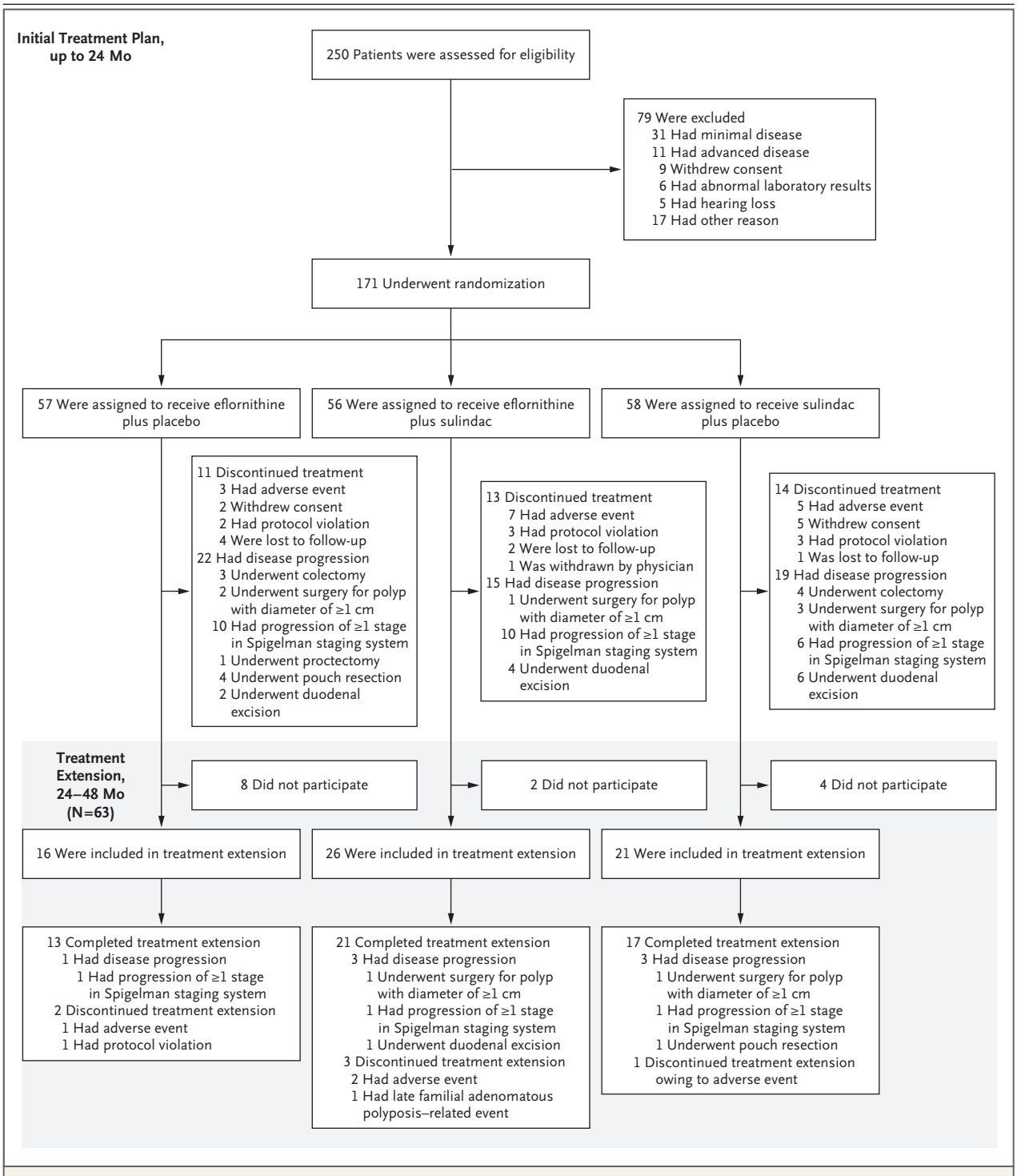


Figure 1. Screening, Randomization, and Follow-up in the Initial Treatment Plan and Treatment Extension.

progression in Spigelman stage underwent intervention for disease progression or had an additional familial adenomatous polyposis–related event, whereas the remaining 22 patients did not have disease progression that was severe enough for intervention.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline in the Intention-to-Treat Population.*

Characteristic	Eflornithine–Sulindac (N=56)	Sulindac (N=58)	Eflornithine (N=57)
Male sex — no. (%)	34 (61)	37 (64)	28 (49)
Age — yr	37.8±13.4	38.1±13.7	39.7±14.8
Precolectomy subgroup	27.4±9.7	22.5±3.7	23.2±8.7
Subgroup with rectal or ileal pouch polyposis after colectomy	38.2±11.6	35.3±11.7	42.4±14.1
Subgroup with duodenal disease	41.5±13.3	44.9±11.4	44.7±12.5
Race — no. (%)†			
White	48 (86)	50 (86)	54 (95)
Black	6 (11)	3 (5)	1 (2)
Other	2 (4)	5 (9)	2 (4)
Body-mass index‡	27.2±5.9	27.2±5.4	28.4±7.7
Time since diagnosis — yr	17.4±10.4	15.5±11.4	19.7±11.5
Surgical status — no. (%)			
Precolectomy	13 (23)	13 (22)	12 (21)
Colectomy with ileorectal anastomosis	13 (23)	19 (33)	21 (37)
Proctocolectomy with ileal pouch–anal anastomosis	28 (50)	21 (36)	18 (32)
Colectomy with ileostomy	2 (4)	5 (9)	6 (11)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† Race was reported by the patients.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

SECONDARY EFFICACY ANALYSES

The results with respect to the secondary efficacy end point of disease progression among the patients in the three surgical subgroups are provided in Table 2 and Figure S1. Among the 37 in the precolectomy subgroup, disease progression occurred in 2 of 12 (17%) in the eflornithine–sulindac group, 6 of 13 (46%) in the sulindac group, and 5 of 12 (42%) in the eflornithine group. Kaplan–Meier estimated mean times to the first event of disease progression were 39.3 months (95% CI, 37.1 to 41.6) in the eflornithine–sulindac group, 25.2 months (95% CI, 24.2 to 26.1) in the sulindac group, and 19.7 months (95% CI, 18.2 to 21.1) in the eflornithine group; the hazard ratio in the eflornithine–sulindac group, as compared with the sulindac group, was 0.30 (95% CI, 0.07 to 1.32), and the hazard ratio in the eflornithine–sulindac group, as compared with the eflornithine group, was 0.20 (95% CI, 0.03 to 1.32) (Fig. S1A). There were no polyposis-related events or surgical procedures in the lower gastrointestinal tract among the patients treated with eflornithine–sulindac in the precolectomy subgroup.

Among the 34 patients with rectal or ileal pouch polyposis after colectomy, disease progression occurred in 4 of 11 (36%) in the eflornithine–sulindac group, 2 of 11 (18%) in the sulindac group, and 5 of 12 (42%) in the eflornithine group. Kaplan–Meier estimated mean times to first disease progression event were 20.9 months (95% CI, 19.8 to 22.0) in the eflornithine–sulindac group, 27.5 months (95% CI, 25.3 to 29.6) in the sulindac group, and 15.7 months (95% CI, 14.9 to 16.6) in the eflornithine group; the hazard ratio in the eflornithine–sulindac group, as compared with the sulindac group, was 2.03 (95% CI, 0.43 to 9.62), and the hazard ratio in the eflornithine–sulindac group, as compared with the eflornithine group, was 0.84 (95% CI, 0.24 to 2.90) (Fig. S1B).

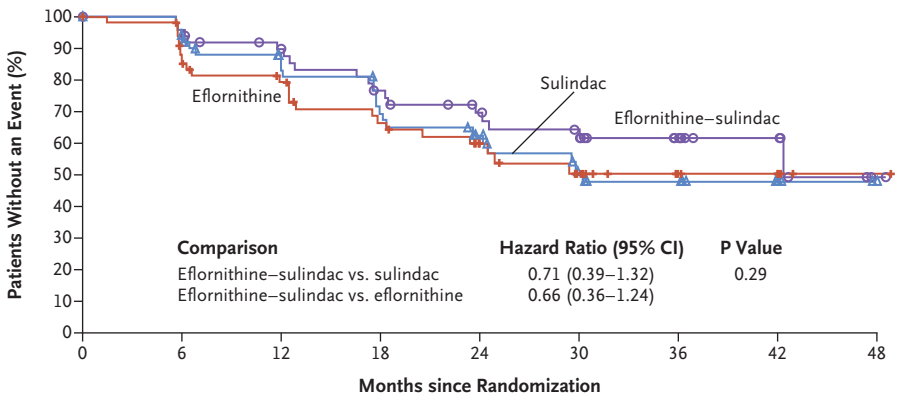
Among the 100 patients with duodenal polyposis, disease progression occurred in 13 of 33

Table 2. Efficacy Outcomes According to Surgical Subgroup and Treatment Group.*

Subgroup and Outcome	Eflornithine–Sulindac (N=56)	Sulindac (N=58)	Eflornithine (N=57)	Hazard Ratio for Disease Progression (95% CI)	
				Eflornithine–Sulindac vs. Sulindac	Eflornithine–Sulindac vs. Eflornithine
Precolectomy subgroup					
No. of patients	12	13	12		
Familial adenomatous polyposis–related event — no. of patients (%)	2 (17)	6 (46)	5 (42)	0.30 (0.07–1.32)	0.20 (0.03–1.32)
Progression of ≥1 stage in Spigelman staging system	2 (17)	1 (8)	2 (17)		
Colectomy or proctocolectomy	0	4 (31)	2 (17)		
Colectomy or proctocolectomy and progression of ≥1 stage in Spigelman staging system	0	0	1 (8)		
Duodenal excision and progression of ≥1 stage in Spigelman staging system	0	1 (8)	0		
Subgroup with rectal or ileal pouch polyposis after colectomy					
No. of patients	11	11	12		
Familial adenomatous polyposis–related events — no. of patients (%)	4 (36)	2 (18)	5 (42)	0.84 (0.24–2.90)	2.03 (0.43–9.62)
Progression of ≥1 stage in Spigelman staging system	3 (27)	0	1 (8)		
Pouch resection	0	1 (9)	2 (17)		
Removal of polyp with diameter of ≥1 cm in rectum or pouch	0	1 (9)	1 (8)		
Proctocolectomy	0	0	1 (8)		
Duodenal excision	1 (9)	0	0		
Subgroup with duodenal polyposis					
No. of patients	33	34	33		
Familial adenomatous polyposis–related events — no. of patients (%)	12 (40)	14 (41)	13 (39)	0.73 (0.34–1.52)	0.76 (0.35–1.64)
Progression in Spigelman stage	5 (15)	3 (9)	7 (21)		
Duodenal excision	4 (12)	6 (18)	2 (6)		
Duodenal excision and progression of ≥1 stage in Spigelman staging system	1 (3)	2 (6)	1 (3)		
Duodenal excision and removal of polyp with diameter of ≥1 cm in rectum or pouch	0	1 (3)	0		
Removal of polyp with diameter of ≥1 cm in rectum or pouch	2 (6)	1 (3)	1 (3)		
Proctocolectomy and removal of polyp with diameter of ≥1 cm in rectum or pouch	0	1 (3)	0		
Pouch resection	0	0	2 (6)		

* The stages in the modified Spigelman duodenal scoring system and classification range from 0 to 4, with higher stages indicating a higher 10-year cumulative risk of duodenal cancer and a higher frequency of esophagogastroduodenoscopy.[31] CI denotes confidence interval.

(39%) in the eflornithine–sulindac group, 14 of 34 (41%) in the sulindac group, and 13 of 33 (39%) in the eflornithine group. Kaplan–Meier estimated mean times to the first event of disease progression were 23.6 months (95% CI, 23.0 to 24.2) in the eflornithine–sulindac group, 21.1 months (95% CI, 20.5 to 21.8) in the sulindac group, and 21.7 months (95% CI, 21.0 to



No. at Risk									
Eflornithine–sulindac	56	48	41	34	28	23	15	8	1
Sulindac	58	47	37	30	24	16	12	6	1
Eflornithine	57	47	39	31	19	13	6	4	1

Figure 2. Kaplan–Meier Curves for Time to the First Familial Adenomatous Polyposis–Related Event (Intention-to-Treat Population).

22.3) in the eflornithine group; the hazard ratio in the eflornithine–sulindac group, as compared with the sulindac group, was 0.72 (95% CI, 0.34 to 1.52), and the hazard ratio in the eflornithine–sulindac group, as compared with the eflornithine group, was 0.76 (95% CI, 0.35 to 1.64) (Fig. S1C). The results of each secondary endpoint evaluation is provided in Table S3.

SAFETY

Treatment-related adverse events were reported by 68% of the patients in the eflornithine–sulindac group, 74% of the patients in the sulindac group, and 55% of the patients in the eflornithine group (Table 3). Most treatment-related adverse events were mild to moderate in severity and resolved with minimal intervention. The most common treatment-related adverse events reported among all the patients were nausea (15%), headache (11%), diarrhea (7%), vomiting (7%), rectal hemorrhage (7%), abdominal pain (7%), flatulence (6%), dyspepsia (5%), and decreased appetite (5%). More patients in the eflornithine–sulindac group than in the monotherapy groups had rash, upper abdominal pain, and erosive gastritis (Table 3). The serious treatment-related adverse events that were reported included acute pancreatitis, nephritis, and psychosis–paranoia (in one patient each in the eflornithine–sulindac group); severe nausea, deep-vein thrombosis, worsening of depression, and spontaneous abortion (in one patient each in the sulindac group); and stroke (in one patient in the eflornithine group). Discontinuation of a trial drug because of adverse events was reported in nine patients (16%) in the eflornithine–sulindac group, six patients (10%) in the sulindac group, and five patients (9%) in the eflornithine group.

DISCUSSION

Familial adenomatous polyposis is a systemic disease, and the ultimate goal of treatment in patients with this condition is to prevent cancer. Delaying progression of colorectal and duodenal polyposis, delaying surgery, and decreasing the procedure-related morbidity, mortality, and effect on quality of life[11-15] are aspirational. The Colorectal Adenoma/Carcinoma Prevention Programme 1 (CAPP1) trial, in which 133 patients with familial adenomatous polyposis underwent randomization, did not show a benefit of 600 mg of aspirin, 30 g of fermentable fiber, or both, as compared with placebo, with regard to polyp burden.[35] Whereas investigators of previous trials reported polyp burden,[21,24-27,29,35] our trial was designed to detect the incidence of disease progression, which encompasses more than polyposis. In our trial, 171 patients with familial adenomatous polyposis underwent randomization, and the trial was powered to detect an incidence of disease progression that was 40 percentage-

Table 3. Adverse Events with an Incidence of at Least 5% in Any Treatment Group.*

Event	Eflornithine–Sulindac (N=56)	Sulindac (N=57)	Eflornithine (N=56)	Total (N=169)
	number of patients (percent)			
Adverse event that occurred during the treatment period	52 (93)	50 (88)	49 (88)	151 (89)
Treatment-related adverse event	38 (68)	42 (74)	31 (55)	111 (66)
Grade ≥3 adverse event that occurred during the treatment period	12 (21)	12 (21)	17 (30)	41 (24)
Treatment-related serious adverse event	3 (5)	4 (7)	1 (2)	8 (5)
Discontinuation of treatment because of a treatment-related adverse event	7 (12)	5 (9)	3 (5)	15 (9)
Death	0	0	0	0
Adverse event of any grade				
Nausea	9 (16)	9 (16)	8 (14)	26 (15)
Headache	3 (5)	7 (12)	8 (14)	18 (11)
Diarrhea	4 (7)	3 (5)	5 (9)	12 (7)
Vomiting	2 (4)	4 (7)	5 (9)	11 (7)
Rectal hemorrhage	4 (7)	4 (7)	3 (5)	11 (7)
Abdominal pain	3 (5)	4 (7)	4 (7)	11 (7)
Flatulence	4 (7)	3 (5)	3 (5)	10 (6)
Dyspepsia	2 (4)	4 (7)	3 (5)	9 (5)
Decreased appetite	2 (4)	4 (7)	3 (5)	9 (5)
Abdominal distension	1 (2)	3 (5)	4 (7)	8 (5)
Fatigue	1 (2)	4 (7)	3 (5)	8 (5)
Hematochezia	2 (4)	2 (4)	4 (7)	8 (5)
Upper abdominal pain	5 (9)	1 (2)	2 (4)	8 (5)
Dizziness	2 (4)	2 (4)	3 (5)	7 (4)
Tinnitus	1 (2)	5 (9)	1 (2)	7 (4)
Pruritus	1 (2)	4 (7)	2 (4)	7 (4)
Rash	6 (11)	0	0	6 (4)
Alopecia	2 (4)	3 (5)	0	5 (3)
Thrombocytopenia	0	3 (5)	1 (2)	4 (2)
Depression	0	3 (5)	1 (2)	4 (2)
Frequent bowel movements	0	1 (2)	3 (5)	4 (2)
Erosive gastritis	3 (5)	0	0	3 (2)

* Adverse events that occurred during the treatment period were defined as any adverse event that occurred after the administration of the first dose of a trial drug through 30 days after the last dose was administered. A treatment-related adverse event was defined as any adverse event that was considered to be possibly, probably, or definitely related to trial drug, as determined by the investigator and reviewed by the medical monitor, both of whom were unaware of the treatment-group assignments. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[33]

points lower with the combination therapy than with monotherapy (the expected overall incidence of familial adenomatous polyposis–related events was 30% with combination therapy and 70% with monotherapy over 2 years). We did not observe that the percentage of patients with disease progression was significantly lower with combination therapy than with either monotherapy. For ethical reasons, all patients received a potentially active drug.

To ensure balance in randomization to the treatment groups, patients were stratified on the

basis of the anatomical site with the highest polyp burden and surgical status (precolectomy [shortest projected time], rectal or ileal pouch polyposis after colectomy [longest projected time], or duodenal polyposis [intermediate projected time]). Among the patients in the precolectomy subgroup, those who received the combination therapy had the lowest incidence of familial adenomatous polyposis–related events, with hazard ratios for disease progression of 0.30 (95% CI, 0.07 to 1.32) for the comparison of eflornithine–sulindac with sulindac and 0.20 (95% CI, 0.03 to 1.32) for the comparison of eflornithine–sulindac with eflornithine. In this subgroup, no patient who received combination therapy had any gastrointestinal polyposis or underwent lower gastrointestinal tract surgery. These data show a possible benefit with combination therapy for patients with familial adenomatous polyposis who have an intact colon. The magnitude of the possible benefit of combination therapy with eflornithine and sulindac observed in this subgroup in our trial is similar to that reported in a trial involving patients with sporadic adenomas, in which the same combination therapy provided a significant benefit over placebo, with a 70% lower risk of metachronous adenomas and more than a 90% lower risk of advanced adenomas.[25] The potential benefit of combination therapy with eflornithine and an NSAID to suppress colorectal polyposis is also supported by the findings in the trial of combination therapy with eflornithine and celecoxib in patients with familial adenomatous polyposis.[24] In that trial, although no significant benefit with combination therapy was observed with respect to the primary end point (polyp number in a defined area of the colorectum), substantial benefit was observed for the secondary end point of global polyp burden in the whole colon. We agree with the conclusion by the authors of that article that this is a more clinically relevant end point and should have been used as the primary end point in their trial.

In our trial, there was no observed treatment benefit with combination therapy in the subgroup of patients who had duodenal polyposis — the group with an intermediate projected time to disease progression. The results of the comparisons between combination therapy and either monotherapy were not significant in the subgroup of patients who had rectal or ileal pouch polyposis after colectomy — the group with the longest projected time to disease progression. The percentage of patients with stage 3 severity of disease according to the InSIGHT classification was greater in the eflornithine–sulindac group than in either monotherapy group, which could have affected the outcome; this possibility suggests that more detailed analyses of these data may be warranted.

Our trial has several limitations. Despite the fact that this trial was larger than previous trials on pharmacologic prevention in patients with familial adenomatous polyposis, it was relatively small, and the 95% confidence intervals for our hazard ratios were wide for this small sample size. Despite the difficulties associated with anticipating the incidence of progression among patients with rare diseases, our data showed that the eflornithine–sulindac group had the expected result with an incidence of 32%. However, the incidences in the eflornithine and sulindac groups were much lower than the predicted 70% that we had estimated on the basis of our literature review. This result may have contributed to the lack of significance between the eflornithine–sulindac group and either monotherapy group. Furthermore, adult patients who had not yet undergone a colectomy are difficult to recruit because most patients with familial adenomatous polyposis are in the need of colectomy by their late teens.[7] Although progression in Spigelman stage was prespecified as an familial adenomatous polyposis–related event and was included as one of the criteria in the primary composite end point in this trial, the Spigelman staging system has not been validated for risk stratification of patients with familial adenomatous polyposis,[36] nor is it ideal for this purpose in its current format.[37,38] This point is underscored in a case–control study involving 18 patients with familial adenomatous polyposis, among whom duodenal cancer developed in 9 despite an endoscopic finding of a Spigelman stage of lower than 4.[39] This study also showed that only two components of the scoring system, duodenal adenoma size and high-grade dysplasia, correlated with duodenal cancer, which underscores the highly subjective nature of this scoring system. We speculate that had the overall change in polyp burden been our end-point measure, as it has been in most previous clinical trials, we would have been able to better capture actual regres-

sion in adenoma burden. The inclusion of 22 patients who had progression in Spigelman stage and did not undergo subsequent endoscopic polyp excision or surgery or have an additional familial adenomatous polyposis–related event may have contributed to a type II error. In this respect, in the absence of cancer in these patients, we may have overestimated disease progression. In our trial, serious adverse events with the combination therapy with eflornithine and sulindac up to 4 years were similar to those with monotherapy, and the majority of adverse events observed in the trial were mild to moderate in severity.

Our trial did not show that the incidence of disease progression was significantly lower with the combination of eflornithine and sulindac than with either drug alone. No patient with an intact colon who received combination therapy underwent surgical intervention. Additional studies that focus on clinical end points in the lower gastrointestinal tract are warranted to better understand the potential of this combination therapy for pharmacologic prevention in specific groups of patients with familial adenomatous polyposis, especially those who have not yet undergone prophylactic colectomy.

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APPENDIX

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