Clinical trial results:
A Double-Blind, Randomized, Phase III Trial of the Safety and Efficacy of CPP-1X/Sulindac Compared With CPP-1X, Sulindac as Single Agents in Patients with Familial Adenomatous Polyposis (FAP)

Summary

EudraCT number	2012-000427-41
Trial protocol	GB DE NL ES BE
Global end of trial date	25 November 2018

Results information

Result version number	v2 (current)
This version publication date	25 June 2020
First version publication date	18 December 2019
Version creation reason	• Correction of full data set Correct site status
Summary attachment (see zip file)	FAP-310_SYNOPSIS (FAP-310 CSR synopsis 20Nov2019.pdf)

Trial information

Trial identification

Sponsor protocol code	CPP FAP-310

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01483144
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cancer Prevention Pharmaceuticals
Sponsor organisation address	1760 E River Road Ste 250, Tucson, United States, 85718
Public contact	Andrew Hadlington, Wessex Pharma Services Ltd., 44 7796394475, Andy.Hadlington@wessexpharma.co.uk
Scientific contact	Andrew Hadlington, Wessex Pharma Services Ltd., 5204982275 7796394475, Andy.Hadlington@wessexpharma.co.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 November 2018
Global end of trial reached?	Yes
Global end of trial date	25 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to determine whether the combination of CPP-1X + sulindac is superior to either treatment individually, sulindac alone or CPP-1X alone, in delaying time to the first occurrence of any FAP-related event in the patient as a whole. This includes: 1) FAP related excisional intervention involving the colon, rectum, pouch, duodenum and/or 2) clinically important events which includes progression to more advanced duodenal polyposis, cancer or death.

Protection of trial subjects:

Subjects were assessed by endoscopy every 6 months to determine if disease progression had occurred. Hearing was monitored every 12 months. Laboratory assessments for hematology, chemistry and urinalysis were done every 6 months. Subjects were contacted monthly to assess any adverse events. Cardiac function was monitored by EKG every 6 months.

Background therapy:

None

Evidence for comparator:

The use of sulindac has been endorsed by health organizations and consensus groups for the suppression of colorectal adenomatous polyps in patients with FAP since 1997. Sulindac has been shown to suppress the development of premalignant colonic polyps in patients with familial adenomatous polyposis. Over the past nearly 20 years, several groups have conducted clinical trials of oral eflornithine in the setting of cancer prevention. A Phase III clinical trial of combination daily oral eflornithine and sulindac for three years versus placebo showed a 70% reduction in total, and greater than 90% reduction in advanced and/or multiple, metachronous colon adenomas. In FAP, a study of eflornithine in combination with celecoxib showed that the combination was not different from celecoxib alone for the primary endpoint (duodenal and colorectal polyp number), but it did show statistically significant reductions in the secondary endpoints of polyp volume and global polyp burden.

Actual start date of recruitment	03 June 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	United States: 103
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Netherlands: 15
Worldwide total number of subjects	171
EEA total number of subjects	52

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	165
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 17 sites in the United States, Canada, Belgium, Germany, the Netherlands, Spain, and the United Kingdom. First subject enrolled in December 2013, with enrollment completed in April 2016.

Pre-assignment

Screening details:

250 subjects were screened. Screen failure reasons included insufficient disease, advanced disease, withdrew consent, other medical conditions, logistical issues, abnormal labs, clinical hearing loss, and no APC mutation.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	CPP-1X + placebo

Arm description:

CPP-1X (750 mg) + placebo

Arm type	Active comparator
Investigational medicinal product name	Eflornithine
Investigational medicinal product code	
Other name	CPP-1X, DFMO
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

750 mg of eflornithine (3 tablets of 250 mg) administered once daily

Investigational medicinal product name	sulindac placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

sulindac placebo tablet administered once daily

Arm title	Sulindac + placebo

Arm description:

Sulindac (150 mg) + placebo

Arm type	Active comparator
Investigational medicinal product name	Sulindac
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

150 mg of sulindac + placebo tablets (3) adminstered once daily

Investigational medicinal product name	Eflornithine placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

3 Eflornithine placebo tablets administered once daily

Arm title	CPP-1X + Sulindac

Arm description:

CPP-1X (750 mg) + sulindac (150 mg)

Arm type	Experimental
Investigational medicinal product name	Eflornithine
Investigational medicinal product code	
Other name	CPP-1X, DFMO
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

750 mg of eflornithine (3 tablets of 250 mg) administered once daily

Investigational medicinal product name	Sulindac
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

150 mg of sulindac + placebo tablets (3) adminstered once daily

Number of subjects in period 1	CPP-1X + placebo	Sulindac + placebo	CPP-1X + Sulindac
Started	57	58	56
Completed	44	43	41
Not completed	13	15	15
Consent withdrawn by subject	2	5	-
Physician decision	-	-	1
Adverse event, non-fatal	4	6	9
Lost to follow-up	4	1	2
Protocol deviation	3	3	3

Baseline characteristics

Reporting groups	
Reporting group title	CPP-1X + placebo
Reporting group description: CPP-1X (750 mg) + placebo	
Reporting group title	Sulindac + placebo
Reporting group description: Sulindac (150 mg) + placebo	
Reporting group title	CPP-1X + Sulindac
Reporting group description: CPP-1X (750 mg) + sulindac (150 mg)	

Reporting group values	CPP-1X + placebo	Sulindac + placebo	CPP-1X + Sulindac
Number of subjects	57	58	56
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
median	39	38	36
full range (min-max)	18 to 71	18 to 71	18 to 65
Gender categorical Units: Subjects			
Female	29	21	22
Male	28	37	34

Reporting group values	Total		
Number of subjects	171		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		

From 65-84 years	0		
85 years and over	0		

Age continuous Units: years median full range (min-max)	- 		
Gender categorical Units: Subjects			
Female	72		
Male	99		

End points

End points reporting groups	
Reporting group title	CPP-1X + placebo
Reporting group description: CPP-1X (750 mg) + placebo	
Reporting group title	Sulindac + placebo
Reporting group description: Sulindac (150 mg) + placebo	
Reporting group title	CPP-1X + Sulindac
Reporting group description: CPP-1X (750 mg) + sulindac (150 mg)	

Primary: Time to first FAP related event (25% percentile)	
End point title	Time to first FAP related event (25% percentile)
End point description:	
End point type	Primary
End point timeframe: Time from randomization to up to first FAP-related event (up to 48 months)	

End point values	CPP-1X + placebo	Sulindac + placebo	CPP-1X + Sulindac	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	58	56	
Units: months				
arithmetic mean (confidence interval 95%)	12.5 (6 to 20.5)	17.7 (6.8 to 23.6)	18.3 (12.2 to 30)	

Attachments (see zip file)	Time to Event ITT/T14_2_1_1_1_T_TTe_Figure.pdf

Statistical analyses	
Statistical analysis title	Hazard ratio for time to FAP related event
Statistical analysis description: stratified log-rank test	
Comparison groups	CPP-1X + placebo v Sulindac + placebo v CPP-1X + Sulindac

Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2898 [1]
Method	stratified score method
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.3

Notes:

[1] - Above p value is in comparison to sulindac. P value in comparison to CPP-1X is p=0.2001

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
All adverse events are to be documented from the day the subject receives his/her first study treatment through 30 days after the subject's off study treatment date (date of last dose).	
Adverse event reporting additional description:	
Adverse events assessed in the clinic at 6 month intervals and by monthly phone contact.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups	
Reporting group title	CPP-1X + placebo
Reporting group description:	
CPP-1X (750 mg) + placebo	
Reporting group title	CPP-1X + Sulindac
Reporting group description:	
CPP-1X (750 mg) + sulindac (150 mg)	
Reporting group title	Sulindac + placebo
Reporting group description:	
Sulindac (150 mg) + placebo	

Serious adverse events	CPP-1X + placebo	CPP-1X + Sulindac	Sulindac + placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 56 (25.00%)	11 / 56 (19.64%)	11 / 57 (19.30%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 56 (1.79%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 56 (0.00%)	1 / 56 (1.79%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma			

subjects affected / exposed	1 / 56 (1.79%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid neoplasm			
subjects affected / exposed	1 / 56 (1.79%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	1 / 56 (1.79%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anastomotic stenosis			
subjects affected / exposed	0 / 56 (0.00%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	1 / 56 (1.79%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative ileus			
subjects affected / exposed	0 / 56 (0.00%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	1 / 56 (1.79%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seroma			
subjects affected / exposed	0 / 56 (0.00%)	1 / 56 (1.79%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			

subjects affected / exposed	1 / 56 (1.79%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound complication			
subjects affected / exposed	0 / 56 (0.00%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence			
subjects affected / exposed	0 / 56 (0.00%)	1 / 56 (1.79%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 56 (0.00%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 56 (1.79%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	1 / 56 (1.79%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 56 (0.00%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 56 (0.00%)	1 / 56 (1.79%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 56 (1.79%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 56 (1.79%)	1 / 56 (1.79%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 56 (0.00%)	1 / 56 (1.79%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 56 (0.00%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 56 (1.79%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 56 (0.00%)	1 / 56 (1.79%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 56 (0.00%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			

subjects affected / exposed	1 / 56 (1.79%)	2 / 56 (3.57%)	2 / 57 (3.51%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	1 / 56 (1.79%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 56 (1.79%)	0 / 56 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary mass			
subjects affected / exposed	0 / 56 (0.00%)	1 / 56 (1.79%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 56 (0.00%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	0 / 56 (0.00%)	1 / 56 (1.79%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephritis			
subjects affected / exposed	0 / 56 (0.00%)	1 / 56 (1.79%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			

subjects affected / exposed	0 / 56 (0.00%)	1 / 56 (1.79%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	0 / 56 (0.00%)	1 / 56 (1.79%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 56 (0.00%)	0 / 56 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 56 (0.00%)	1 / 56 (1.79%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	CPP-1X + placebo	CPP-1X + Sulindac	Sulindac + placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 56 (87.50%)	52 / 56 (92.86%)	50 / 57 (87.72%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 56 (10.71%)	4 / 56 (7.14%)	4 / 57 (7.02%)
occurrences (all)	11	5	6
Headache			
subjects affected / exposed	5 / 56 (8.93%)	8 / 56 (14.29%)	11 / 57 (19.30%)
occurrences (all)	6	11	12
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 56 (14.29%)	4 / 56 (7.14%)	8 / 57 (14.04%)
occurrences (all)	11	5	9
Influenza like illness			

subjects affected / exposed	5 / 56 (8.93%)	5 / 56 (8.93%)	3 / 57 (5.26%)
occurrences (all)	7	7	4
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	2 / 56 (3.57%)	1 / 56 (1.79%)	4 / 57 (7.02%)
occurrences (all)	2	1	4
Tinnitus			
subjects affected / exposed	1 / 56 (1.79%)	2 / 56 (3.57%)	6 / 57 (10.53%)
occurrences (all)	1	2	7
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	5 / 56 (8.93%)	2 / 56 (3.57%)	3 / 57 (5.26%)
occurrences (all)	6	2	3
Abdominal pain			
subjects affected / exposed	4 / 56 (7.14%)	8 / 56 (14.29%)	8 / 57 (14.04%)
occurrences (all)	4	12	9
Abdominal pain upper			
subjects affected / exposed	4 / 56 (7.14%)	7 / 56 (12.50%)	1 / 57 (1.75%)
occurrences (all)	4	8	1
Constipation			
subjects affected / exposed	5 / 56 (8.93%)	3 / 56 (5.36%)	2 / 57 (3.51%)
occurrences (all)	6	4	3
Diarrhoea			
subjects affected / exposed	8 / 56 (14.29%)	7 / 56 (12.50%)	6 / 57 (10.53%)
occurrences (all)	12	8	9
Dyspepsia			
subjects affected / exposed	5 / 56 (8.93%)	2 / 56 (3.57%)	5 / 57 (8.77%)
occurrences (all)	5	4	6
Flatulence			
subjects affected / exposed	3 / 56 (5.36%)	5 / 56 (8.93%)	3 / 57 (5.26%)
occurrences (all)	3	5	3
Haematochezia			
subjects affected / exposed	6 / 56 (10.71%)	6 / 56 (10.71%)	2 / 57 (3.51%)
occurrences (all)	8	10	3
Nausea			

subjects affected / exposed	9 / 56 (16.07%)	12 / 56 (21.43%)	12 / 57 (21.05%)
occurrences (all)	14	18	20
Rectal haemorrhage			
subjects affected / exposed	4 / 56 (7.14%)	7 / 56 (12.50%)	7 / 57 (12.28%)
occurrences (all)	8	8	7
Vomiting			
subjects affected / exposed	7 / 56 (12.50%)	6 / 56 (10.71%)	10 / 57 (17.54%)
occurrences (all)	10	8	23
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 56 (10.71%)	3 / 56 (5.36%)	4 / 57 (7.02%)
occurrences (all)	6	3	4
Oropharyngeal pain			
subjects affected / exposed	5 / 56 (8.93%)	5 / 56 (8.93%)	1 / 57 (1.75%)
occurrences (all)	5	6	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 56 (0.00%)	2 / 56 (3.57%)	3 / 57 (5.26%)
occurrences (all)	0	2	3
Pruritus			
subjects affected / exposed	2 / 56 (3.57%)	3 / 56 (5.36%)	4 / 57 (7.02%)
occurrences (all)	2	3	4
Rash			
subjects affected / exposed	0 / 56 (0.00%)	6 / 56 (10.71%)	2 / 57 (3.51%)
occurrences (all)	0	6	2
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 56 (1.79%)	2 / 56 (3.57%)	4 / 57 (7.02%)
occurrences (all)	1	2	6
Depression			
subjects affected / exposed	1 / 56 (1.79%)	1 / 56 (1.79%)	4 / 57 (7.02%)
occurrences (all)	1	1	3
Insomnia			
subjects affected / exposed	2 / 56 (3.57%)	1 / 56 (1.79%)	4 / 57 (7.02%)
occurrences (all)	2	1	4
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	5 / 56 (8.93%)	4 / 56 (7.14%)	3 / 57 (5.26%)
occurrences (all)	8	6	3
Back pain			
subjects affected / exposed	5 / 56 (8.93%)	5 / 56 (8.93%)	3 / 57 (5.26%)
occurrences (all)	6	8	3
Musculoskeletal pain			
subjects affected / exposed	4 / 56 (7.14%)	0 / 56 (0.00%)	2 / 57 (3.51%)
occurrences (all)	5	0	2
Myalgia			
subjects affected / exposed	2 / 56 (3.57%)	4 / 56 (7.14%)	1 / 57 (1.75%)
occurrences (all)	2	4	1
Neck pain			
subjects affected / exposed	1 / 56 (1.79%)	3 / 56 (5.36%)	0 / 57 (0.00%)
occurrences (all)	1	3	0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	4 / 56 (7.14%)	7 / 56 (12.50%)	5 / 57 (8.77%)
occurrences (all)	4	9	6
Influenza			
subjects affected / exposed	3 / 56 (5.36%)	4 / 56 (7.14%)	3 / 57 (5.26%)
occurrences (all)	5	4	3
Nasopharyngitis			
subjects affected / exposed	10 / 56 (17.86%)	6 / 56 (10.71%)	4 / 57 (7.02%)
occurrences (all)	14	12	4
Sinusitis			
subjects affected / exposed	5 / 56 (8.93%)	4 / 56 (7.14%)	2 / 57 (3.51%)
occurrences (all)	5	4	3
Upper respiratory tract infection			
subjects affected / exposed	2 / 56 (3.57%)	8 / 56 (14.29%)	8 / 57 (14.04%)
occurrences (all)	3	14	10
Urinary tract infection			
subjects affected / exposed	4 / 56 (7.14%)	2 / 56 (3.57%)	2 / 57 (3.51%)
occurrences (all)	5	2	2
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	4 / 56 (7.14%) 4	2 / 56 (3.57%) 2	5 / 57 (8.77%) 5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 May 2014	Update to cardiovascular inclusion criteria, change to maximum weekly dose of aspirin allowed, clarification of determination of post-menopausal status, update to cardiovascular safety monitoring, and timing of EKG, and clarification of when rectal/pouch polyps need to be removed at baseline.
14 March 2016	Adds treatment extension of an additional 12 months and clarification of the futility analysis.
21 July 2017	Increases treatment extension to a maximum of 48 months. Pregnancy management/reporting procedures updated. Update to the statistical analysis section.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

FAP related events were based on a composite endpoint. Exploratory analyses indicate that not all endpoints included were clinically meaningful.

Notes: