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)

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal tract disorders congenital
Study type	Interventional

Summary

ID

NL-OMON44874

Source
ToetsingOnline

Brief title
CPP FAP-310

Condition

- Gastrointestinal tract disorders congenital

Synonym
FAMILIAL ADENOMATOUS POLYPOSIS, FAP

Research involving

Human

Sponsors and support

Primary sponsor: Cancer Prevention Pharmaceuticals Inc.
Source(s) of monetary or material Support: Cancer Prevention Pharmaceuticals;Inc

Intervention

Keyword: CPP-1X/Sulindac, FAP (Familial Adenomatous Polyposis), Safety and Efficacy

Outcome measures

Primary outcome

Primary Efficacy End Point is 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.

The timepoint(s) of evaluation of this endpoint:

Subjects will be assessed at 3, 6, 12, 18, and 24 months. Endoscopies (upper

and lower GI) will be carried out every 6 months.

For subjects participating in the treatment extension up to 2 additional

endosocpies will be performed (month 30 and 36).

For subjects participating in the prolonged treatment extension (month 36-48)

up to 2 additional endoscopies will be performed (month 42 and 48).

Secondary outcome

The secondary efficacy outcome in this study will include the following:

1. To evaluate the potentially effect modifying properties of :

a. Presence or absence of an ODC polymorphism

b. The excretion of 4 urinary polyamines (diacetylspermine,

n1-acetylspermidine, n8-acetylspermidine and decarboxylated SAM)

Other secondary outcomes will include the following:

1. Safety outcomes will be assessed by summary analysis of adverse events and

clinical laboratory abnormalities.

2. Pharmacokinetic outcomes will be assessed by evaluating the population

pharmacokinetics for CPP-1X (eflornithine) and sulindac.

3. Evaluate tissue and dietary polyamine levels.

4. Patient reported quality of life will be evaluated using HRQoL and patient

utilities.

5. A pilot evaluation of an FAP-specific assessment, the time to the first

FAP-related beneficent event, will be studied. This will involve analyzing

the endoscopic polyposis data for regression of pre-colectomy colorectal

polyposis, rectal/pouch polyposis, and regression of duodenal polyposis.

Study description

Background summary

Familial Adenomatous Polyposis (FAP) is a genetic disorder in which hundreds of polyps are present in the colon. These polyps often occur at a young age. The risk arising from the polyps is that cancer develops and this increases with age. Eventually, almost everyone who has FAP will get colon cancer.

The current standard treatment consists of prophylactic removal of the large intestine or the colon and rectum, followed by proctoscopic surgical intervention in which the polyps to be removed for the rest of their lives every 6-12 months
Prophylactic removal of the colon and where appropriate the rectosigmoid do not "heal" the patients. FAP-related disease remains a major problem and leads to significant morbidity and mortality. Surgical intervention is marginally effective and there are no approved pharmacological agents.
The extension of the time to clinical worsening (FAP-related operation, duodenal polyposis, cancer and death) is important in relation to the morbidity and mortality of this genetic disease.
The use of low dose sulindac and CPP-1X may be able to extend to the occurrence of clinically important FAP-related events over time. This creates a clinical benefit and morbidity.

Study objective

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.

Study design

A DOUBLE-BLIND, RANDOMIZED,SAFETY AND EFFICACY PHASE III TRIAL

Intervention

Patients will be randomized 1:1:1 to one of three treatment groups:
1) CPP-1X Plus Sulindac
-three (3) 250 mg CPP-1X tablets plus one (1) 150 mg Sulindac tablet
2) CPP-1X Plus Sulindac-Placebo
-three (3) 250 mg CPP-1X tablets plus one (1) Sulindac-Placebo tablet
3) CPP-1X-Placebo Plus Sulindac
-three (3) CPP-1X-Placebo tablets plus one (1) 150 mg Sulindac tablet

Daily oral dosing for a maximum duration of 48 months. 4 tablets taken once daily with food same time of day.

Study burden and risks

The potential risks associated with study participation are those risks and disadvantages as associated with the study medication (amongst others Cardiac

risk and Ototoxicity risk), Gastro-intestinal risk and the risks associated with bloodsampling.
In relation with the Cardiac Risk, all patients will undergo a baseline medical history evaluation and ECG for cardiovascular disease risk assessment. Only subjects meeting the inclusion criteria will be enrolled in the study.
On-study cardiac risk assessments, for each patient, will take place throughout the study via ongoing adverse event assessments and periodic EKG evaluations at baseline, and months 3, 6, 12, 18 and 24 (end of treatment). For subjects participating in the treatment extension up to 4 additional ECG will be performed (Month 30, 36, 42 and 48)

Concerning the Ototoxicity Risk all patients will undergo air conduction audiometry for hearing impairment as part of the screening process and at months 12 and 24 (end of treatment). For subjects participating in the treatment extension additonal audiometry tests will be performed at month 36 and month 48(EoT).

Patient diaries will indicate the presence of symptoms and will instruct the patient to contact the treating doctor for assessment. Furthermore the patient will undergo a clinical assessment for ototoxicity adverse events symptoms by the research nurse or other medically qualified individual.
Gastrointestinal Risk: Endoscopies will be done by an experienced study team member. Also patient*s diaries will indicate presence of symptoms and will instruct the patient to contact the treating doctor for assessment and the patient will undergo a clinical assessment for gastrointestinal adverse events symptoms by the research nurse
As a general Safety Evaluation will be done continuously throughout the study and will be followed from the start of treatment through 30 days after treatment discontinuation. Serious adverse events will be followed until resolved or returned to baseline, even if longer than 30 days from the subject*s off study treatment or off study date.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Subjects (male and female), * 18 years
1. Diagnosis of phenotypic classical FAP with disease involvement of the duodenum and/or colon/rectum/pouch.
a. Genotype: APC mutation (with or without family history) required
b. Classical FAP Phenotype: 100*s to 1,000*s of colorectal adenomatous polyps, usually appearing in teenage years
2. UGI endoscopy/LGI endoscopy (proctoscopy/colonoscopy) performed within 30 days of randomization.
3. Patients with an intact colon/rectum and prophylactic surgery is being considered as a stratification site.
4. Rectal/pouch polyposis as a stratification site as follows:
4.a At least three years since colectomy with IRA/proctocolectomy with pouch, and demonstrating polyposis as defined by Stage 1, 2, 3, of the proposed InSiGHT 2011 Staging System (protocol Appendix B) and summarized as follows:
Stage 1: 10-25 polyps, all < 5 mm
Stage 2: 10-25 polyps, at least one > 1 cm
Stage 3: >25 polyps amenable to complete removal, or any incompletely removed sessile polyp, or any prior evidence of high grade dysplasia, even if completely removed. [Note: For staging purposes only.]
4.b For all subjects, any rectal/pouch polyps > 5 mm must be excised at *baseline*.
5. Duodenal polyposis as a stratification site; one or more of the following:
5.a Current Spigelman Stage 3 or 4. (Refer to protocol Appendix A for Modified Spigelman Score and Classification table).
5.b Prior surgical endoscopic intervention within the past six months for Spigelman Stage 3 or 4 that may have been down staged to Spigelman 1 or 2.

6. Hematopoietic Status (within 30 days prior to randomization):
a) No significant hematologic abnormalities
b) WBC at least 3000/mm3
c) Platelet count at least 100,000/mm3
d) Hemoglobin at least 10.0 g/dL
e) No history of clinical coagulopathy
7. Hepatic Status (within 30 days prior to randomization):
a) Bilirubin no greater than 1.5 times ULN
b) AST and ALT no greater than 1.5 times ULN
c) Alkaline phosphatase no greater than 1.5 times ULN
8. Renal Status (within 30 days prior to randomization):
a) Creatinine no greater than 1.5 times ULN
9. Hearing:
a) No clinically significant hearing loss, defined in Section 6.2, number 9.
10. If female, neither pregnant nor lactating.
11. Negative pregnancy test if female of child-bearing potential. Fertile patients must use effective contraception. Confirmation of postmenopausal status unless surgically sterile.
12. Absence of gross blood in stool; red blood on toilet paper only acceptable.
13. No discrete gastric or duodenal ulcer greater than 5 mm within the past year except Helicobacter pylori-related peptic ulcer disease treated with antibiotics.
14. No invasive malignancy within the past 5 years except resected non-melanomatous skin cancer, papillary thyroid cancer, or precancerous cervical dysplasia.
15. No other significant medical or psychiatric problems that would preclude study participation or interfere with capacity to give informed consent.
16. Use of 81 to 100 mg daily aspirin or up to 700 mg aspirin not more than once a week are eligible.
17. No concurrent warfarin, fluconazole, lithium, Pradaxa® or other direct thrombin inhibitors, Plavix®, cyclosporine, other NSAIDs (such as ibuprofen, aspirin, diflunisal), diuretics (furosemide and thiazides), DMSO, methotrexate, probenecid, propoxyphene hydrochloride, Tylenol® (acetaminophen) preparations containing aspirin or cytotoxic chemotherapy drugs.
18. Willingness to forego concurrent use of supplements containing omega-3 fatty acids, corticosteroids, non-steroidal anti-inflammatory drugs or other FAP directed drug therapy.
19. Able to provide written informed consent and follow protocol requirements.

Exclusion criteria

1. Prior pelvic irradiation.
2. Patients receiving oral corticosteroids within 30 days of enrollment.
3. Treatment with other investigational agents in the prior 4 weeks.
4. Use of other non-steroidal anti-inflammatory drugs (such as ibuprofen) exceeding 4 days per month, in the prior 6 weeks.
5. Regular use of aspirin in excess of 700 mg per week.
6. Treatment with other FAP directed drug therapy (including sulindac or celecoxib, fish oil) within 12 weeks of study enrollment.

7. Hypersensitivity to cyclooxygenase-2 inhibitors, sulfonamides, NSAIDs, or salicylates; NSAID associated symptoms of gastritis.
8. Patients must not have cardiovascular disease risk factors as defined below.
* Uncontrolled high blood pressure (systolic blood pressure > 150 mm Hg;
* Unstable angina;
* History of documented myocardial infarction or cerebrovascular accident;
* New York Heart Association Class III or IV heart failure (Refer to Appendix C);
* Known uncontrolled hyperlipidemia defined as LDL-C * 190 mg/dL or triglycerides * 500 mg/dL.
9. Patients with significant hearing loss are not eligible for study participation as defined below.
* Hearing loss that affects everyday life and/or for which a hearing aid is required.
10. Colon/rectum/pouch with high grade dysplasia or cancer on biopsy or a large polyp (>1 cm) not amenable to complete removal.
11. Duodenal cancer on biopsy.
12. Intra-abdominal desmoid disease, stage III or IV (staging criteria in protocol Appendix D).
13. Inability to provide informed consent.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-01-2014
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	eflornithine
Product type:	Medicine
Brand name:	sulindac
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	29-07-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-01-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-09-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-04-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-04-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-04-2017

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-08-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-08-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Other	01483144
EudraCT	EUCTR2012-000427-41-NL
CCMO	NL45085.018.13

Study results

Results posted: 25-11-2019

First publication
20-11-2019