RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE, EFFICACY, SAFETY AND TOLERABILITY OF EPA-FFA GASTRO-RESISTANT CAPSULES, IN PATIENTS WITH FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

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Primary Objective* To determine the efficacy of EPA-FFA gastro-resistant capsules in patients with FAP in reducing polypectomy.Secondary Objectives* To evaluate the clinical disease progression.* To evaluate the long-term safety and tolerability of...

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

Summary

ID

NL-OMON55587

Source
ToetsingOnline

Brief title
EPA-FFA in FAP

Condition

- Gastrointestinal tract disorders congenital
- Gastrointestinal neoplasms malignant and unspecified

Synonym
FAP, hereditary development of polyps in colon

Research involving
Human

Sponsors and support

Primary sponsor: SLA Pharma
Source(s) of monetary or material Support: SLA Pharma

Intervention

Keyword: FAP, multicenter, placebo-controlled, randomised

Outcome measures

Primary outcome

Primary Endpoint

* Total number of polypectomies (polyps >5 mm in the rectum) conducted during

the 24 months study period.

Safety Endpoints

The safety analysis will be conducted in all randomised subjects receiving at

least one dose.

* The number and proportion of subjects with AEs.

* The number of subjects requiring hospitalisation.

* Assessment of clinical laboratory parameters.

* Assessment of vital signs.

Secondary outcome

Secondary Endpoints

* Change in polyp number at 24 months assessed by blinded review of video

records.

* Change in score on the InSiGHT Polyposis Staging System (IPSS) at 24 months.

* Number of subjects requiring surgical intervention (not including polypectomies).

* Total number of polypectomies (polyps >5mm in the rectum) conducted at 6 months, 12 months, 18 months.

* Change in polyp number at 6 months, 12 months, 18 months assessed by blinded review of video records.

* Change in score on the InSiGHT Polyposis Staging System (IPSS) at 6 months, 12 months, 18 months.

* Time to surgical intervention (not including polypectomies).

* Change in score on the Spigelman Classification of Duodenal Polyposis at 24 months.

* Patient*s Global Impression of Improvement (PGI-I) at Months 6, 12, 18 and 24.

Study description

Background summary

Familial Adenomatous Polyposis (FAP) is an inherited susceptibility to diffuse colorectal adenomas and colorectal carcinoma, occurring in close to 100% of unresected colons, and caused by a germline mutation in the APC gene located on the long arm of chromosome 5 [Kinzler et al 1996]. To prevent cancer development, it is recommended that patients with FAP undergo colectomy with ileo-anal or ileo-rectal anastomosis (or colectomy and end-ileostomy) at a socially convenient time before polyp progression to malignancy and before the age of 25. Patients with the attenuated FAP phenotype, often associated with mutations at the 5* terminus (exon 4 and proximally) [Spiro et al 1993], have fewer polyps and may often delay colectomy.

The molecular events leading to the development of CRC from polyps are characterised by an imbalance in cell proliferation and apoptosis (natural cell death) from alterations in those genes involved in colonic mucosal homeostasis.

Furthermore, evidence exists to show that differences are present in the cell kinetics of the colonic mucosa of patients who are polyp formers and those who are not. Those patients who have a predisposition to form colonic adenomas are thought to have a generalised decreased level of apoptosis and higher rates of cell proliferation throughout the colon [Steinbach et al 1946-1953].

Colectomy removes the bulk of the polyps in FAP, therefore significantly reducing the cancer risk, yet retains the native rectum in situ allowing a good functional outcome and avoiding stoma formation. Subsequent proctectomy is indicated when polyp burden is frequently high in the remaining rectum, if large highly dysplastic polyps occur, or if frank malignancy develops. Proctocolectomy also significantly reduces the cancer risk with the removal of the colon and rectum. A pouch fashioned from the terminal ileum can be created, and anastomosed to the anus. Routine endoscopic surveillance is also required with timings dependent on the extent of the disease, with polyp ablation as necessary.

It has been suggested that omega-3 PUFAs in fish oil can modulate the high levels of colonicmucosal cell proliferation rates associated with sporadic colonic adenomas [Anti M et al 1994] and furthermore, work at St George*s Hospital Medical School, London, has shown significant beneficial effects of cell proliferation and apoptosis rates on the colonic mucosa of patients with a history of colonic adenomas using a highly purified, form of EPA as the free fatty acid [Courtney et al 2005].

Fatty acids are either saturated, monounsaturated or polyunsaturated. Some omega-6 and omega-3 polyunsaturated fatty acids; are *essential* fatty acids, i.e. they cannot be made in the human body and therefore must be obtained from dietary sources. The Western diet is abundant in omega-6 fatty acids (e.g. corn oil, sunflower oil). Humans lack the necessary enzyme to synthesise certainomega-3 fatty acids and so they must be obtained from separate dietary sources. Whilst *-linolenic acid can be obtained from certain vegetable sources, the two main omega-3 fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are obtained principally from fish and fish oils. There is evidence of the benefit of fish oils in the prevention of cardiovascular disease [Gerdes et al 1994] and there is also the suggestion that they may be useful in the prevention of other conditions such as prostatic cancer and colorectal cancer [Boyle and Langman 2000].

The mechanism(s) of the anti-neoplastic activity of EPA-FFA is not fully understood. Several mechanisms have been postulated including modulation of cyclooxygenase (COX) activity,
promotion of apoptosis by increasing reactive oxygen species production and alteration of cellsurface receptor function by changing lipid raft behaviour. EPA can act as an alternative, poorly utilised substrate (rather than arachidonic acid prevalent in Western diets) for the COX enzymes (including COX-2) leading to decreased pro-tumorigenic prostaglandin E2 production.

Recently, EPA treatment has been demonstrated to reduce PGE2 levels in rodent colorectal mucosa and in mouse colorectal cancer liver metastases (Hawcroft et al 2010). In this respect, it has similar activity to the coxibs. However, EPA drives 3-series prostaglandin and thromboxane production by COX-1 which is believed to explain the anti-platelet activity of EPA, in contrast to the coxibs which promote a thrombogenic state secondary to endothelial cell COX-2 inhibition and unopposed thromboxane A2 activity in platelets.

The effects of EPA-FFA on polyps have been investigated in the Multiple intestinal neoplasia (Min) mouse. The Min mouse has a mutation of the tumour suppressor gene (APC). This confers a predisposition to form polyps in the small and large intestines which develop rapidly within the first 12 weeks of life. It thus provides an animal model of FAP in which the effects of potential chemopreventative interventions can be examined. ApcMin/+ and corresponding wild-type mice were fed control diet (Ctrl) or diets containing either EPA-FFA 2.5% or EPA-FFA 5%, for 12 weeks while monitoring food intake and body weight. Tissues were collected for macroscopic, microscopic, immunohistochemical and mucosal fatty acids analyses. Blood was collected to measure lipid peroxidation levels. Both EPA-FFA diets protected from the cachexia observed among ApcMin/+ animals fed Ctrl diet ($P < 0.0054$), in conjunction with a significant decrease in lipid peroxidation in the treated arms. Compared to Ctrl, EPA-FFA 2.5% and 5% dramatically repressed polyp formation (by 71.5% and 78.6%, respectively, $P < 0.0001$) and reduced polyp load (by 82.5% and 93.4%, respectively, $P < 0.0001$). Polyps <1mm were predominantly found in the 5% EPA-FFA treatment arm while those measuring 1-3 mm were more frequent in the Ctrl group ($P < 0.0001$). In the EPAFFA treated mice, arachidonic acid in gastrointestinal mucosa was replaced by EPA ($P < 0.0001$), this was associated with a significant reduction of COX-2. In the EPA-FFA treated arms, *-catenin nuclear translocation was reduced (small intestine) or absent (colon), while a significant decrease in proliferation was observed in the entire intestine with a concomitant increase in apoptosis (Fini et al 2010).

A chemoprevention trial in FAP patients has been conducted using the EPA-FFA gastro resistant capsules. This was a single-centre, double-blind, randomised, placebo-controlled study conducted in adult subjects with a confirmed diagnosis of FAP and previous colectomy with ileo-rectal anastomosis. Consenting subjects, aged 18 or older, with a diagnosis of FAP and an evaluable rectal segment having 3 or more rectal polyps *2mm in size (within an area of the rectum that could be tattooed) were recruited. Subjects satisfying the entry criteria were randomised (1:1) to receive one of two treatments: placebo twice daily or 500mg EPA, as the free fatty acid, twice daily (total daily dose 2g) for 6 months. In total, 58 subjects were randomised, 29 to the placebo group and 29 to the EPA treatment group. Few subjects withdrew prematurely from the study, (3 in placebo and 2 in the EPA treatment group). For all subjects in the placebo group the reason for withdrawal was adverse events or clinically significant laboratory result requiring discontinuation. In the EPA group failure to tolerate study drug and other (specifically that the subject did not

attend the 6 months visit) were the reasons given. The study demonstrated a statistically significant reduction in number of
polyps (p=0.0046 Full analysis set) in a focal area of the rectum following six months treatment with EPA compared to placebo. Statistically significant differences between the EPA treatment group and placebo group were found for percentage change in number of polyps, percentage change in total polyp diameter and global rectal polyp burden (as assessed by the expert review panel). Treatment with EPA resulted in an increase in rectal mucosal content of EPA and DPA relative toother fatty acids. This is in keeping with the proposition that increased levels of EPA lead to a change in production of local mediators involved in the development of polyps. Overall, EPA was well-tolerated in this population (West et al 2010).

extracted from protocol 5.1

Study objective

Primary Objective
* To determine the efficacy of EPA-FFA gastro-resistant capsules in patients with FAP in reducing polypectomy.

Secondary Objectives
* To evaluate the clinical disease progression.
* To evaluate the long-term safety and tolerability of EPA-FFA.

Study design

2 year randomised, double-blind, placebo-controlled, parallel group study to determine the safety and efficacy of EPA-FFA gastro resistant
capsules in FAP.

Intervention

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Study burden and risks

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Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Must give written informed consent.
2. Male or female subjects, 18 to 65 years of age.
3. Known diagnosis of FAP defined as those with a pathogenic APC mutation anastomosis.
4. Patients have had a previous colectomy with an ileo-rectal anastomosis or an ileal pouch- anal anastomosis with a rectal remnant of * 2cm
5. Classified stage 1-3 on InSiGHT Polyposis Staging System (IPSS).
6. Subjects must show a willingness to abstain from regular use of nonsteroidal anti-inflammatory medication for the trial. A cardioprotective dose of aspirin (75mg-100mg) will be permitted.

Exclusion criteria

1. In subjects with previous ileo-rectal anastomosis * 20 polyps > 5mm in the rectum.
2. Subjects unwilling to have regular endoscopic examination.
3. Subjects who are due to undergo gastro-intestinal surgery related to FAP.
4. History of invasive carcinoma in the past 3 years.

5. History of pelvic radiation.
6. Known allergic reaction or intolerant to fish or fish oils.
7. Known allergic reaction to excipients of IMP and placebo.
8. Subjects who are pregnant or breast-feeding at screening.
9. Subjects taking aspirin or other non-steroidal anti-inflammatory drugs on a regular basis other than low dose (75mg-100mg) cardioprotective dose.
10. Subjects taking NSAIDs regularly in the 3 months prior to entry (other than low dose aspirin).
11. Subjects taking NSAID, 5-aminosalicylic acid (5-ASA or mesalamine).
12. Subjects who are taking other fish-oil supplements (e.g. cod liver oil) who are unwilling to stop them for the duration of the study. Subjects previously taking fish oil must have a washout period of 2 months prior to study enrolment.
13. Subjects who are taking warfarin or other anticoagulants.
14. Experimental agents must have been discontinued at least 8 weeks prior to screening for a period equivalent to 5 half-lives of the agent (whichever is longer).
15. Subjects suffering from known disorders of clotting and blood coagulation.
16. Subjects who have significant abnormalities on their screening blood tests.
17. Subjects with gastrointestinal malabsorptive disease.
18. Subjects with uncontrolled hypercholesterolaemia.
19. Subjects who are deemed mentally incompetent, or have a history of anorexia nervosa or bulimia.
20. Subjects who will be unavailable for the duration of the trial, deemed unable to comply with the requirements of the study protocol, likely to be noncompliant with the protocol, or who are felt to be unsuitable by the Investigator for any other reason.
21. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless surgically sterile must use effective contraception (either combined estrogen and progestogen containing hormonal contraception associated with inhibition of ovulation [oral, intravaginal, transdermal], progestogen only hormonal contraception associated with inhibition of ovulation [oral, injectable, implantable], intrauterine device [IUD], intrauterine hormone-releasing system [IUS], vasectomised partner, sexual abstinence (only considered an acceptable method of contraception when it is in line with the subjects* usual and preferred lifestyle), combination of male condom with either cap, diaphragm or sponge with spermicide [double barrier methods]), and willing and able to continue contraception for 1 month after the last administration of
IMP. Women using oral contraception must have started using it at least 2 months prior to screening. Women are not considered to be of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels that have beenconfirmed to be in the *postmenopausal range*. Or have had a surgical bilateral oophorectomy (with or without hysterectomy) or bilateral tubal ligation at least six weeks before the screening visit. In case of oophorectomy alone, the reproductive status of the woman should have been

confirmed by follow up hormone level assessment.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-12-2018
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	not available yet
Generic name:	EPA-FFA

Ethics review

Approved WMO Date:	13-04-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-08-2018

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-05-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-09-2021
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
EudraCT	EUCTR2017-002809-34-NL
CCMO	NL63731.018.18