Rifaximin delayed release (400 mg tablet) for the prevention of recurrent acute diverticulitis and diverticular complications. A phase II, multicenter, double-blind, placebo-controlled, randomized clinical trial.

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to evaluate the safety and efficacy of two different doses of a delayed release formulation of rifaximin (Rifaximin-EIR) for the prevention of recurrence of diverticulitis and diverticular complications in patients with a recent episode of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Diverticular disorders
Study type	Interventional

Summary

ID

NL-OMON48624

Source
ToetsingOnline

Brief title
ROAD

Condition

- Diverticular disorders

Synonym
diverticular inflammation, Diverticulitis

Research involving

Human

Sponsors and support

Primary sponsor: Alfasigma SpA
Source(s) of monetary or material Support: Alfasigma SpA

Intervention

Keyword: Diverticulitis, Prevention, Rifaximin

Outcome measures

Primary outcome

Primary endpoint

Rate of patients with recurrence of diverticulitis or diverticular

complications over the 12-month treatment period.

Definitions:

a) Diverticulitis is defined as the presence of:

* abdominal pain or tenderness at physical examination

plus

* at least one of the following:

* fever

* leukocytosis and/or C-reactive Protein (CRP) above the upper limit of normal

plus

* diagnosis confirmation with imaging of diverticulitis at CT or US.

* Recurrent diverticulitis defined as a new episode of diverticulitis after

previous clinical remission.

* Diverticular complications are the following: diverticula-associated bleeding, abscess, fistula, perforation, peritonitis, obstruction.

Complications will be diagnosed and documented per specific center procedures.

Primary endpoint and event date will be adjudicated by the Investigator based on the collected documentation.

Secondary outcome

Key secondary endpoint:

Rate of patients who, over the 12-month treatment period, have had an acute episode of prolonged (at least 24 hours) left lower quadrant abdominal pain plus concomitant leukocytosis or elevation of serum CRP (i.e. above the upper limit of normal) with or without CT or US imaging confirming acute diverticulitis.

Additional secondary endpoints (evaluated throughout the entire study treatment period)

* Time to diverticulitis recurrence/complication.

* Rate of patients with diverticulitis-associated fever as a component of the primary endpoint.

* Change from baseline of the following symptoms will be assessed:

* left-lower quadrant abdominal pain (intensity and duration of episodes);

* bowel habits.

* Number of days in a year with left-lower quadrant abdominal pain, number of days in a year with any abdominal pain, number of weeks in a year with episodes of left-lower quadrant abdominal pain lasting *24 hours, and number of weeks in a year with bloating.

* Rate of any hospitalization for diverticulitis.

* Rate of hospitalization for diverticulitis without surgery.

* Rate of elective surgery for diverticulitis.

* Rate of emergency surgery for diverticulitis.

* Change in Quality of Life.

Exploratory secondary endpoint

Change in faecal calprotectin levels (only in selected sites).

Study description

Background summary

It has been hypothesized that colonic microbiota changes may play a key role in the pathogenesis of acute diverticulitis. Previous proof-of-concept studies suggest that rifaximin, a low-absorbable oral antibiotic, may be beneficial for prevention of acute diverticulitis recurrence by modulating the gut microflora.

Study objective

to evaluate the safety and efficacy of two different doses of a delayed release formulation of rifaximin (Rifaximin-EIR) for the prevention of recurrence of diverticulitis and diverticular complications in patients with a recent episode of diverticulitis, in remission at the time of screening.

Study design

Multicentre, double-blind, placebo-controlled, randomized clinical trial.

Intervention

* Group A: Rifaximin-EIR 800 mg b.i.d. (i.e. 2x400 mg tablets twice a day; total daily dose: 1600 mg) for 10 consecutive days a month, for 12 months.
* Group B: Rifaximin-EIR 400 mg b.i.d. (i.e. 1x400 mg tablet plus 1 placebo tablet twice a day; total daily dose: 800 mg) for 10 consecutive days a month, for 12 months.
* Group C: Placebo b.i.d. (i.e. 2xplacebo tablets twice a day) for 10 consecutive days a month, for 12 months.

Study burden and risks

No specific risks are associated with the administration of the study drug. After administration of Rifaximin the following reactions have been reported most often: dizziness, headache, gastrointestinal symptoms such as abdominal pain, bloating, constipation, diarrhoea, nausea, vomiting, flatulence, rectal tenesmus (i.e. anal pain during defecation), urge to defecate and fever (high fever). Skin rash (redness of the skin) has also been reported.

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

1) Men and women aged 18-80 years at screening visit (V1).
2) Female participants must be:
*of non-childbearing potential, i.e.: i) post-menopausal (at least 2 years without spontaneous menses), or ii) surgically sterile (bilateral tubal occlusion, or hysterectomy), or iii) ablation of both ovaries)
or
*of childbearing potential with a negative pregnancy test result at screening and randomization AND agreeing to use a highly effective method of contraception (i.e. with failure rate of less than 1% per year) until 72 hours after the last dose of investigational drug of the entire study.
Note 1: Based on Clinical Trial Facilitation Group recommendations, highly effective methods of contraception are the following:
i)intrauterine device (IUD);
ii)intrauterine hormone-releasing systems (IUS); or;
iii)combined hormonal contraceptives (i.e. estrogen and progestogen) in oral, intravaginal or transdermal form, with inhibition of ovulation as primary mode of action; or
iv)progestogen-only hormonal contraceptives in oral, injectable or implantable form, with inhibition of ovulation as primary mode of action; or
v)absolute and continuous sexual abstinence.
Note 2: In each case of delayed menstrual period (over one months between menstruations), female participants of child-bearing potential will be strongly recommended a confirmation of absence of pregnancy. This recommendation applies also to women of child-bearing potential with infrequent or irregular menstrual cycles.
3)A previous documented episode of diverticulitis between 30 and 180 days prior to screening (V1).
Diverticulitis is defined as the presence of
*abdominal pain or tenderness
plus
*at least one of the following:
*fever or
*leukocytosis and/or high serum C-Reactive Protein (CRP) levels (above the upper limit of normal)
plus
*diagnosis confirmation with imaging of diverticulitis at computed tomography (CT), ultrasound (US) or colonoscopy. Note: per scientific guidelines, colonoscopy is not recommended and will not be accepted to diagnose acute diverticulitis recurrence throughout the study, however a colonoscopy diagnosis of acute diverticulitis can be

accepted retrospectively for enrolment purposes only.
4)Patients must be in clinical remission from acute diverticulitis at the screening (V1). Patients with symptomatic uncomplicated diverticular disease (SUDD, i.e. patients with mild abdominal pain or tenderness but no clinically significant inflammation (i.e. no increased number of leukocytes) at screening (V1) can be enrolled.
5)Patients accepting to provide and legally capable of providing free and informed consent to all procedures included in the protocol

Exclusion criteria

1) History of 2 or more acute diverticulitis episodes or history of any diverticular complication.
2)Any documented current organic disease of the gastrointestinal tract other than diverticulosis (including but not limited to: severe esophagitis, active peptic ulcer, acute gastritis, pancreatitis, hepatitis, cancer, angiodysplasia, familial adenomatous polyposis, intestinal obstruction [including partial intestinal obstruction], any enteritis [also including those associated with fever and/or bloody stools], etc.).
3)Laboratory signs of significant acute inflammation (consistent with unresolved diverticulitis) or signs/ symptoms of diverticular complications.
4)Diagnosis or history of inflammatory bowel disease (or other conditions associated with ulcerative lesions of the intestinal tract).
5)History of polypectomy for early colon cancer confirmed after polypectomy or history of any large bowel (including anal canal) or small bowel resection for any reason. Patients with history of polypectomy for non-cancerous adenomas only can be enrolled.
6)Patients with positive Clostridium difficile toxin stool assay.
7)Health conditions requiring continuous or intermittent treatment with systemic steroids and/or biologic or non-biologic immunosuppressive or immunomodulatory agents (e.g. autoimmune diseases, etc.).
8)Use of marketed rifaximin (or neomycin or other low-absorbable oral antibiotics) during or after the previous episode of acute diverticulitis.
9) Treatment with the following drugs within 28 days prior to randomization: pharmaceutical probiotics (functional food is allowed), systemic antibiotics, mesalazine (a.k.a. mesalamine, 5-ASA), NSAIDs (also including aspirin greater than 100 mg a day), opioid drugs, warfarin, systemic steroids (inhaled steroids are permitted), cyclosporine or any other non-biologic immunosuppressive or immunomodulatory agent.
10) Biologic immunosuppressive or immunomodulatory agent within 180 days prior to randomization (V2).
11) Cancer (excluding non-melanoma skin cancer) and/or need of any anti-cancer treatment (also including radiotherapy) within 5 years.
12) Severe hepatic impairment (i.e. Child-Pugh B or C).
13) Severe kidney impairment (i.e. estimated glomerular filtration rate (GFR) <30 ml/min).
14) Any other current significant health condition (e.g. cardiovascular, respiratory, renal, hepatic, neurologic, psychiatric, hematologic, oncologic, immune, muscle and joint, etc.) that in the Investigator*s judgement may:
i) jeopardize the patient*s safe participation in the trial; or

ii) make unlikely the patient*s completion of the study; or
iii) make unlikely the patient*s compliance with the study procedures (e.g. highly anticipated need of non-permitted treatments, significant disability, terminal illness, etc.).
15) History of hypersensitivity to rifaximin, rifamycin-derivatives or any of the rifaximin delayed release excipients or placebo (see list in the protocol).
16) History of any alcohol or drug abuse or dependence within the last year.
17) Women who are pregnant, breast-feeding or planning a pregnancy during the trial period.
18) Subjects who have participated in another drug clinical trial/taken any other investigational drug within 6 months prior to randomization.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-06-2019
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	nvt
Generic name:	rifaximin

Ethics review

Approved WMO Date:	10-04-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-01-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-09-2019
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	EUCTR2017-002708-28-NL
ClinicalTrials.gov	NCT03106922
CCMO	NL64312.029.18