Phase III, Parallel-group, Placebo Controlled, Double-blind, Randomized, Multicenter International Study to Investigate the Safety and Efficacy of Propionyl-L-carnitine Hydrochloride (ST 261) Modified Release Tablets in Patients Affected by Mild Ulcerative Colitis under Oral Stable Treatment

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON37764

Source
ToetsingOnline

Brief title
Propionyl-L-carnitine in Ulcerative Colitis

Condition

- Gastrointestinal inflammatory conditions

Synonym
ulcerative colitis - inflammation of colon

Research involving
Human

Sponsors and support

Primary sponsor: Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.
Source(s) of monetary or material Support: sponsor van de studie

Intervention

Keyword: efficacy, inflammation of colon, safety, ulcerative colitis

Outcome measures

Primary outcome

The primary endpoint will be the clinical/endoscopic remission defined as a Disease Activity Index at the end of treatment <= 2 with rectal bleeding sub-score = 0 and no other individual sub-score >1.

Secondary outcome

Secondary endpoints will be:

• Rectal bleeding evaluation by means of DAI sub-score (from 0 to 3).

• Stool frequency evaluation by means of DAI sub-score (from 0 to 3).

A clinical response for each of these parameters is defined as a sub-score improvement of at least 1 point over baseline.

The histological response to the treatments, defined as an improvement of the Histological Index (HI - see Appendix III) of at least 1 point at the end of the study (a final HI score smaller of equal to 1 will be defined as a histological remission) will also be evaluated as additional exploratory end-point.

The serum C-reactive protein and Fibrinogen will be monitored to investigate possible correlation between clinical/endoscopic outcome and serum level of these inflammatory markers.

A validated specific questionnaire, the SIBDQ by McMaster University, will be administered to evaluate changes in patients* Quality of Life.

The safety and tolerability of the treatments will be investigated through AEs recording, vital signs, ECG and laboratory evaluation.

Study description

Background summary

The drug propionyl-L-carnitine hydrochloride is since 1998 marketed under the name dromos ® (tablets or powder for injection) for the indication of occlusion of the arterial blood vessels of the lower limbs and chronic heart failure (improvement of cardiac activity). The active ingredient in the drug's dromos of propionyl-L-carnitine hydrochloride, a substance that normally the human body itself produces. The drug propionyl-L-carnitine hydrochloride is used in this study, is given in the form of a new formulation of modified release tablets (tablets that selectively dissolve in the colon). This new formula has been administered to patients suffering from mild to moderate ulcerative colitis to the positive effects of safety and efficacy testing versus placebo.

Study objective

Ulcerative colitis is an inflammatory disease that affects the colon. The extent and severity of the disease may vary: it is possible that the disease only the rectum (the lower part of the colon) found, but the disease may extend over the entire length of the colon.
Ulcerative colitis is one of the "inflammatory diseases of the gut," a generic term used to refer to a group of chronic inflammatory diseases of unknown origin and which affect the intestinal tract.
Generally known patients suffering from ulcerative colitis periods of relapse (worsening of inflammation) alternating with periods of disease remission.

During relapse, symptoms such as abdominal pain, diarrhea and rectal bleeding worse.
During remission take these symptoms. In general, remissions for after using drugs or surgery, but occasionally they can occur spontaneously.
Since there are currently no drugs that can cure ulcerative colitis, is to a drug treatment to achieve the following: remission induction, and retain the quality of life of the patient improved.
Medicines used for this standard are as follows: anti-inflammatory drugs such as 5-aminosalycilzuurverbindingen (5-ASA), corticosteroids and immunomodulators.
Ulcerative colitis can be mild, moderate or severe forms occur, depending on the clinical, endoscopic (direct observation of the intestinal tract) and histological (microscopic analysis of intestinal tissue) observations. This difference determines the most appropriate therapeutic choice for each patient.
The object of this clinical study is whether the administration of investigational drug propionyl L carnitine hydrochloride can lead to improved lighting of the disease in patients with mild ulcerative colitis and who are already treated with a standard drugs (excluding corticosteroids and immunomodulators). With the research described below, we especially want to collect data on the efficacy and tolerability of propionyl-L-carnitine hydrochloride.
This study is "controlled versus placebo ', ie a group of patients receives a substance which has no pharmacological effect. The use of a placebo is methodologically necessary to the possible beneficial effects of the investigational drug to correctly evaluate without bias from external factors.
The primary objective of this study is to compare the two treatment groups (propionyl-L-carnitine hydrochloride (ST 261) tablets of modified release 1 g / day vs.. Placebo) with respect to the number of patients with disease remission at the end of 8 weeks of treatment. Evaluation of the safety and tolerability of ST 261 is a primary objective of the study.
The secondary objectives are the maintenance of remission after treatment four weeks was interrupted, the histological changes, improving the symptoms of the disease (subscores) and the overall quality of life as measured using the Short Inflammatory Bowel Disease Questionnaire (SIBDQ).

Study design

This study is carried out in 'parallel' groups, ie patients in the study treated with only one of two different treatments.

This study is a 'double blind' study, this means that neither the patient nor the clinical investigator knows which treatment the patient has been assigned. They will only know this when the investigation is complete, but nevertheless, there is guaranteed that, if necessary, it is possible to immediately find out which treatment was given. The 'blind' condition is ensured by the fact that the placebo tablets look similar when the drug under investigation, but the placebo tablets contain no active ingredient.

This study is a randomized 'study: ie the assignment of one of the two treatment groups based on random, statistical criteria that are not affected by the physician nor the patient condition. The chance that one of the two treatment groups is assigned is the same.

Intervention

See "Description and assessment of strain and risk"

Study burden and risks

If the patient decides to participate in the study, then in this research study, administration of these treatments provide:
• 1 g of propionyl L-carnitine hydrochloride per day by mouth (orally);
• 1 g placebo daily by mouth (orally).
The chance that one of the two study treatments provided is given is about 50/50.
All patients will be 8 weeks long to take 2 tablets daily (one morning and one evening), regardless of the treatment group to which they belong.
The study lasts 12 weeks (a treatment for 8 weeks and 4 weeks without treatment).

The following procedures, the patient underwent
If the patient agrees to participate in this study, under he / she performs an initial check to determine whether his / her condition matches the criteria for the study. During that inspection, the investigator or authorized person of the medical staff his / her questions about his / her medical history. During the audit, he / she is a thorough investigation, including the following:
• a blood sample of 11 ml;
• give a urine sample;
• a medical examination including measurement of your vital signs (blood pressure, weight, height, heart rate);
• an endoscopic examination of the large intestine (using a rectal scope), including four biopsies will be taken (small pieces of the wall of the intestine for microscopic examination);
• an electrocardiogram;
• in women of childbearing age, there will be a blood test be performed to exclude a pregnancy;
• it will make him / her ask for a questionnaire consisting of 10 questions that assessed the quality of life.
If he / she meet the criteria for inclusion in the study, then he / she gets an electronic device (electronic diary) which is similar to a smartphone. He / she will receive instructions for this and they will ask him + her all day to write down the following information:
• Frequency of bowel movements per day (number of bowel movements);
• presence of blood in the stool;

• number of tablets taken.
Furthermore, the patient is given a box containing the active drug or placebo that hij.zij twice a day, before breakfast and before dinner, orally should take. Each box contains 4 blisters of 8 tablets each, a total of 32 tablets for treatment for 14 days (two weeks) plus 2 additional days (if necessary).
After 2 weeks, the patient investigator of another 2 boxes for a further 4 weeks of treatment plus 4 additional days. When the patient to the hospital at week 6 comes back before the planned visit, he / she is the last box for treatment of two weeks plus two extra days. At each visit (weeks 2, 6 and 8) will be him / her ask any unused tablets to the researcher to return.
Apart from the first control mentioned above, are for the study with 4 additional visits after 2, 6, 8 and 12 weeks will take place.
During these visits take place the following controls:
• a blood sample of 11 ml (at 2 and 8 weeks, and only after 12 weeks for any abnormal values **to follow);
• give a urine sample (at 2 and 8 weeks, and only after 12 weeks for any abnormal values **to follow);
• a medical examination at all visits, including monitoring your vital signs (blood pressure, weight, height, heart rate);
• an endoscopic examination of the large intestine (using a rectal scope), including four biopsies will be taken (only after 8 weeks);
• an electrocardiogram (at 2 and 8 weeks, and only after 12 weeks for any abnormal values **to follow);
• a questionnaire on the quality of life (after 8 and 12 weeks);
• women of childbearing age, a blood test will be performed to rule out a pregnancy (after 12 weeks [follow-up visit]).
Since the blood and urine samples for analysis to an external, central laboratory (Esoterix, Mechelen, Belgium) will be sent, it may be that the physician for additional samples ask if he / she sees fit if the blood and urine samples lost or damage which would hit some incorrect values **could be determined.

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. Have read the Information for the Patient and signed the Informed Consent Form.
2. Age comprised between 18 and 75 included.
3. Diagnosis of active ulcerative colitis confirmed endoscopically (pancolonoscopy) and histologically. A new pancolonoscopy is required if documented evidence of having performed it within the previous 12 months is not available. If available, only a new partial colonoscopy for the visualization of the affected part of the colon is required for the evaluation of the baseline DAI score.
4. Rectal bleeding and stool frequency sub-scores have to be evaluated in occasion of the first patient*s screening study visit (on the basis of the patient*s memory of the episodes occurred during the previous two weeks, and considering the worst condition). At this time the rectal bleeding score must be at least 1.
These two sub-scores will be re-evaluated (according to a paper diary recording) during the three days preceding the preparation for the baseline (pre-treatment) partial colonoscopy, to be performed as closest as possible to the conclusion of the screening period.
Sub-scores recorded in occasion of the baseline (pre-treatment) partial colonoscopy will be utilised for the calculation of the baseline Disease Activity Index (DAI) score.
At this time, patients are considered suitable for randomization if they have a Disease Activity index comprised between 3 and 6 inclusive (mild ulcerative colitis), with a rectal bleeding sub-score of at least 1.
5. Stable background oral aminosalycilates (mesalazine, balsalazide, olsalazine) or sulfasalazine standard therapy for greater than or equal to 4 weeks prior to screening assessments.
6. If female, not pregnant or nursing.
7. For women of childbearing potential (WOCBP), willingness to avoid a pregnancy during the treatment period and for at least 4 weeks from the last dose of drug.

A WOCBP is defined as any female who has experienced menarche and who has not undergone successful surgical sterilisation (hysterectomy, bilateral tubal ligation or bilateral ovariectomy) or is not postmenopausal (defined as amenorrhoea >12 consecutive months).

WOCBP should use an efficient method of birth control for the entire duration of the trial and until the first menses after a 30-day period after the last dose of trial medication. They must be on a stable regimen, for at least 1 month, of oral contraceptives, contraceptive implant or depot injection, contraceptive patch, intrauterine device (IUD), or condom and spermicidal agent. The patient will be informed about the results of the pregnancy test and of the allowed method of contraception and its duration.

Exclusion criteria

1. Crohn*s disease and indeterminate colitis.
2. Current or previous (in the last 10 days preceding the screening) use of systemic corticosteroids.
3. Use of systemic antibiotics in the last 10 days preceding the screening.
4. Use of systemic NSAIDs on a repeat basis in the last 10 days preceding the screening.
5. Use of probiotics started within 10 days preceding the screening. A stable regimen from at least 10 days prior to screening is allowed but the patient must be willing to continue up to the end of the study.
6. Patients previously treated with biological agents have to be excluded, as well as patients treated with immunosuppressants within the last 6 weeks preceding the screening.
7. Stool culture positive for enteric pathogens (eg, Shigella, Salmonella, Yersinia, Campylobacter), Parasites (i.e. Amoebae, Coccidia, Giardia, Helminths) or toxins (C.difficile).
8. Significantly impaired liver, renal, pulmonary or cardiovascular function as assessed by the investigator.
9. History of colon resection.
10. Diverticulitis, symptomatic diverticulosis.
11. Active peptic ulcer disease.
12. Proctitis (extent of inflammation <15 cm from the anus).
13. Bleeding disorders (alterations of the coagulation factors or any concurrent other disease possibly causing digestive apparatus bleeding).
14. Rectal therapy with any therapeutic enemas or suppositories with the exception of those required for endoscopy during the 10 days preceding the screening.
15. Active or chronic infection(s) or malignancies.
16. Known hypersensitivity to the active ingredient and excipients of the study drug.
17. Simultaneous participation in another clinical trial, or participation in any clinical trial involving investigational drugs within 3 months from enrolment into the present study.
18. Any physical or psychological condition in a patient that could let the investigator suspect his/her poor compliance.
19. Patients treated with L-carnitine or its esters derivatives during the three months preceding the screening.

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):	15-03-2013
Enrollment:	35
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Dromos
Generic name:	Propionyl-L-carnitine

Ethics review

Approved WMO Date:	25-01-2012
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	24-04-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO	

Date:	27-08-2012
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	22-11-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	08-01-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	16-01-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	22-01-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	18-04-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2011-004765-32-NL
CCMO	NL39147.058.12