Randomized, double-blind, double-dummy, placebo-controlled, Phase III clinical trial on the efficacy and safety of a 12-weeks add-on treatment with LT-02 (gastro-resistant phosphatidylcholine granules) vs. placebo in patients with ulcerative colitis refractory to standard treatment with mesalamine

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Primary:• To prove the superiority of a 12-week add-on treatment with 3.2 g/daygastro-resistant phosphatidylcholine granules (LT-02) in at least one of twodifferent dosing regimens versus LT-02 placebo for the induction ofremission in patients with...

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

Summary

ID

NL-OMON42292

Source
ToetsingOnline

Brief title
PCG-2/UCA

Condition

- Gastrointestinal inflammatory conditions

Synonym
Colitis Ulcerosa, Crohn's disease

Research involving
Human

Sponsors and support

Primary sponsor: Dr. Falk Pharma
Source(s) of monetary or material Support: Dr. Falk Pharma GmbH

Intervention

Keyword: Colitis ulcerosa, mesalamin- refractaire, Phosphatidylcholine, remission

Outcome measures

Primary outcome

Percentage of patients in deep remission (defined as mDAI Score <= 1 with a score of *0* points for rectal bleeding and stool frequency, and >= 1 point reduction from baseline in the mucosal appearance score) at week 12 (LOCF).

Secondary outcome

Double-blind (12-week) and optional open-label (12-week) phase:

• Percentage of patients in remission (defined as mDAI Score <= 2 with no score > 1) at week 12 (LOCF),

• Percentage of patients with clinical improvement in mDAI defined as a decrease of >= 3 points vs. total score at baseline at week 12 (LOCF),

• Total mDAI and its subscores and their changes in the course of the trial,

• Total Clinical Activity Index acc. to Rachmilewitz (CAI) and its subscores and their changes in the course of the trial,

• Percentage of patients with clinical remission (defined as CAI <= 4, with stool

frequency and rectal bleeding subscores of *0*) in the course of the trial,

• Percentage of patients with clinical improvement (CAI) defined as a decrease of >= 3 points compared to baseline in the course of the trial,

• Times to first resolution of clinical symptoms,

• Number of stools per week,

• Number of bloody stools per week,

• Number of days with urgency per week,

• Percentage of patients with mucosal healing (defined as a mDAI mucosal appearance score of *<= 1* at week 12 (LOCF) associated with a decrease of >= 1 point compared to baseline),

• Percentage of patients with improved mDAI mucosal appearance score at week 12 (LOCF),

• Endoscopic Index acc. to Rachmilewitz (EI) compared to baseline at week 12 (LOCF),

• HI in the course of the trial,

• Percentage of patients with histologic remission (HI <= 1) at week 12 (LOCF),

• Percentage of patients with improved HI at week 12 (LOCF),

• Physician's Global Assessment (PGA),

• Patients quality of life,

• Work Productivity and Activity Impairment (WPAI),

• Patient*s Global Satisfaction.

Open-label phase (only):

• Percentage of patients in deep remission at week 12 (LOCF) of OL phase.

Study description

Background summary

A disturbed mucosal barrier is thought to be an initiating factor of UC, enabling attacks from commensal colonic bacteria that lead to mucosal inflammation.62 In healthy subjects, intestinal mucosal cells are protected against colonic bacteria and other injurious contents of the gastrointestinal lumen by a surface barrier which consists in part of a continuous, hydrophobic and adherent mucus layer.4 This mucus consists of a hydrated polymeric gel with a thickness of 50-500 µm,42,66 with < 10% proteins, carbohydrates and lipids.2 Phospholipids were found to form a continuous layer at the luminal side of the mucus gel, within the mucus as liposome-like aggregates and as a monolayer at the surface of the mucosal cells.4,34 They are largely responsible for establishing the hydrophobic surface and play a key role in the barrier properties of the underlying tissue.42
Phosphatidylcholine is considered the predominant phospholipid species present in the distal intestinal mucus.5,7,10,12 By in vitro and in vivo experiments in mice and rats it was demonstrated that PC is actively secreted into the ileum. This secretion is stimulated by bile salts. The absorption of bile salts attaches PC to the mucosal wall. PC is then moved continuously by colonic activity from cecum to rectum. Therefore, the rectum is considered as the last area supplied with PC.11
A significantly lower concentration of PC in the ileal and colonic mucus from patients with UC compared to patients with Crohn*s disease and to controls was shown by Braun et al.6
The observed deficiency of intestinal mucus PC in UC patients and the cell protective and anti-inflammatory properties of PC led to the assumption of a potential clinical activity for exogenous PC in UC. It was hypothesized that daily oral administration and subsequent gastro-resistant release of PC into the ileum can restore the low intestinal PC

concentration
and the protective mucus barrier function and consecutively reduce ulceration and
inflammation due to commensal bacteria, toxins and foreign bodies. The natural flow of PC
from the ileum to the rectum would be restored. To test this hypothesis, a new therapeutic
strategy with PC supplementation to the colonic mucus was developed. A PC preparation
derived from soy lecithin was formulated into granules of microcrystalline cellulose matrix
with gastric acid resistant coating for delayed-release in the intestine. Based on the gastroresistant
formulation, PC is protected from degradation by gastric and pancreatic fluids, thereby potentially reducing the systemic uptake and increasing the local availability in the
intestine.
First results with the to-be-marketed formulation LT-02, containing >= 94% PC as active
ingredient in gastro-resistant granules, in the Phase II study LT-02-UC-01 confirmed the
medical hypothesis and benefit of treating the PC deficiency in patients with UC. The current
Phase III study will be performed to further investigate the clinical efficacy and safety of
LT-02 in the treatment of UC.

Study objective

Primary:
• To prove the superiority of a 12-week add-on treatment with 3.2 g/day gastro-resistant phosphatidylcholine granules (LT-02) in at least one of two different dosing regimens versus LT-02 placebo for the induction of remission in patients with ulcerative colitis (UC) refractory to standard treatment with mesalamine.

Secondary:
• To study safety and tolerability in the form of adverse events (AEs) and laboratory parameters,
• To compare two different dosing regimens of LT-02,
• To assess patients* quality of life.

Open-label sub-study:
• To induce remission of UC in patients not in remission at week 12 or in patients who were prematurely withdrawn >= 8 weeks after randomization due to lack of efficacy without showing clinical response.

Study design

This is a double-blind, double-dummy, randomized, placebo-controlled, multicenter,
comparative, 12-week, confirmative Phase III clinical trial. The trial will be conducted with three arms in the form of a parallel group comparison and will serve to compare oral daily add-on treatment with 3.2 g phosphatidylcholine (LT-02, gastro-resistant granules) in two different dosing regimens versus placebo (LT-02 Placebo, gastro-resistant granules) for the induction of remission in UC patients non-responsive to standard mesalamine treatment. The trial will be performed according to a 2-stage group-sequential adaptive design with potential sample size adjustment and treatment arm selection after the planned interim analysis.
Screening phase:
During 7 up to 10 days prior to baseline, the non-response to a standard treatment with >= 2.4 g/d mesalamine (or therapeutic equivalent) will be confirmed. Patients will complete a daily diary during the screening period while continuing the current oral (and if applicable also rectal) treatment with mesalamine at a stable dose of >= 2.4 g/day (or therapeutic equivalent).
Double-blind, double-dummy, randomized (1:1:1) treatment phase:
Eligible patients will be randomized to receive a 12-week, double-blind, doubledummy
add-on treatment to stable dosage of concomitant oral mesalamine
>= 2.4 g/d (or therapeutic equivalent) with:
Group A: 0.8 g PC in LT-02 four-times daily (QID) with additional placebo sachets taken with morning and evening dose
Group B: 1.6 g PC in LT-02 twice daily (BID) with placebo sachets taken during lunchtime and afternoon doses
Group C: LT-02 placebo QID
Randomization will be stratified by patient*s 5-ASA pre-treatment, i.e., *>= 2.4 g/d mesalamine (or therapeutic equivalent) for >= 6 weeks prior to baseline?* (*yes* vs *no*).
Treatment schedule:

Study Arm	Morning (2 sachets)	Lunchtime (1 sachet)	Afternoon (1 sachet)	Evening (2 sachets)
Group A	0.8 g PC	Placebo	0.8 g PC	0.8 g PC	Placebo
Group B	0.8 g PC	0.8 g PC	Placebo	Placebo	0.8 g PC	0.8 g PC
Group C	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo

Note: One sachet LT-02 contains gastro-resistant granules with 0.8 g PC, one sachet LT-02 Placebo contains
PC-free gastro-resistant granules
The dose, formulation, and intake regimen of oral mesalamine used within the 6 weeks prior to baseline has to be kept stable throughout the complete treatment phase.
Follow-up phase:
All patients completing the trial and coming into remission will have the option to enter a double-blind, placebo-controlled maintenance of remission trial for treatment with LT-02 or placebo for up to 48-weeks (trial code: PCG-4/UCR; EudraCT No.: 2013-001205-84). All other patients completing the trial and who are not in remission or who were prematurely withdrawn >= 8 weeks after randomization due to lack of efficacy and with no clinical improvement in modified Disease Activity Index (mDAI) defined as a total decrease of > 1 point in the sum of the subscores 1, 2, and 4 compared to baseline in mDAI at End of treatment (EOT)/Withdrawal visit, will have the option to enter an open-label induction of remission sub-study for treatment with LT-02 (PCG-5/OLT). Otherwise, patients will be followed-up 4 weeks after EOT/Withdrawal visit.
Open-label (OL) sub-study:
During the OL sub-study (PCG-5/OLT), patients will receive a 12-week, openlabel, uncontrolled treatment with 1.6 g PC in LT-02 BID as add-on treatment to a stable dose of >= 2.4 g/d mesalamine (or therapeutic equivalent).

Intervention

LT-02 (gastro-resistant granules containing 0.8 g phosphatidylcholine [PC] per sachet) as add-on therapy to a standard dose of >= 2.4 g/d mesalamine (or therapeutic equivalent)

Study burden and risks

During the study, the patients have to undergo the following procedures: pregnancy test (if applicable), physical exam (4x), max 3 endospies including biopsies, questionnaires (every visit), diary (every visit), drawing of blood (all visits), stool samples (every visit) and answering question eg. medical history, adverse events, use of co-medication (all visits).

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

Principle Inclusion criteria: ;- Men or women, 18 to 70 years of age, ;- Established diagnosis of UC, based on clinical history, exclusion of infectious causes, and characteristic endoscopic and histologic findings, ;- Active UC with disease extent >= 15 cm (proctitis only patients to be excluded), confirmed by endoscopy and histology,;- Mesalamine (5-ASA) refractory disease,;- Elevated stool calprotectin at screening.;Inclusion criteria for open-label sub-study: ;The following inclusion criterion will apply only to the open label sub-study: ;1. Patients not in remission of UC at week 12, or patients withdrawn >= 8 weeks after randomization due to lack of efficacy and ;showing no clinical improvement.

Exclusion criteria

Principle Exclusion criteria: ;- Crohn's disease, indeterminate colitis, ischemic colitis, radiation colitis, microscopic colitis (i.e., collagenous colitis and lymphocytic colitis), ;diverticular disease associated colitis, ;- Colon resection, ;- Evidence of infectious colitis (e.g., pathogenic bacteria or Clostridium difficile toxin in stool culture at screening), ;- Other inflammatory or bleeding disorders of the colon and intestine, or diseases that may cause diarrhea or gastrointestinal bleeding, ;- History or presence of ischemic heart disease, myocardial infarction, peripheral arterial disease, ischemic stroke, or transient ischemic attack, ;- Treatment with steroids (oral, inhalative, or intravenous [IV]), cyclosporine or tacrolimus

within last 4 weeks prior to randomization, ;- Treatment with methotrexate within last 6 weeks prior to randomization, ;- Treatment with TNF-alpha-antagonists, azathioprine, 6-mercaptopurine, or anti-integrin therapy within last 8 weeks prior to randomization, ;- Treatment with rectal corticosteroid formulation within last 2 weeks prior to randomization, ;- Concomitant treatment with coumarins (e.g., phenprocoumon), ;- Existing or intended pregnancy or breast-feeding.

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:	Pending
Start date (anticipated):	01-03-2014
Enrollment:	40
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	LT-02
Generic name:	Gastro-resistant phosphatidylcholine granules
Product type:	Medicine
Brand name:	Mesalamine
Generic name:	Mesalamine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	14-04-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-09-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-01-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-08-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-09-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2012-003702-27-NL
CCMO	NL48120.091.14