Randomized, double-blind, double-dummy, placebo-controlled, Phase III clinical trial on the efficacy and safety of a 48-weeks treatment with gastro-resistant phosphatidylcholine (LT-02) versus placebo versus mesalamine for maintenance of remission in patients with ulcerative colitis

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Primary:* To prove the superiority of a 48-weeks treatment with 3.2 g/day delayedreleasephosphatidylcholine (LT-02) versus placebo for the maintenance ofremission in patients with ulcerative colitis (UC)Secondary:* To study safety and tolerability...

Ethical review	Not approved
Status	Will not start
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON42465

Source
ToetsingOnline

Brief title
PCG-4/UCR

Condition

- Gastrointestinal inflammatory conditions

Synonym
Colitis Ulcerosa, remission

Research involving
Human

Sponsors and support

Primary sponsor: Dr Falk Pharma GmbH
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 who are relapse-free and are not a treatment failure

after 48 weeks of treatment. Relapse is defined as a rectal bleeding score of

*1 and a mucosal appearance score of *2 as described in the mDAI score.

Treatment failure is defined as premature withdrawal, experiencing UC flare,

or need for other UC treatment

Secondary outcome

Secondary efficacy variables for the DB phase:

* Mean change from baseline in the total mDAI at V6/EOT.

* Percentage of patients maintaining remission defined as a mDAI score *2

with no subscore >1 at V6/EOT visit,

* Number and percentage of patients in each level of change from baseline in

the mDAI stool frequency subscore at V2-V5, and V6/EOT,

* Number and percentage of patients in each level of change from baseline in

the mDAI rectal bleeding subscore at V2-V5, and V6/EOT,

* Number and percentage of patients in each level of change from baseline in the mDAI Physician*s rating of disease subscore at V2-V5, and V6/EOT,

* Time to clinical relapse or discontinuation,

* Number and percentage of patients in each level of change from baseline in the mDAI mucosal appearance subscore at V6/EOT,

Total mDAI and change in mDAI clinical subscores in the course of the DB phase,

* Percentage of patients with endoscopic remission defined as mDAI mucosal appearance score of *1,

* Total and change in Clinical Activity Index acc. to Rachmilewitz (CAI) and its subscores in the course of the DB phase,

* Number and percentage of patients in each level of change from baseline in the CAI in the course of the DB phase,

* Percentage of patients in clinical remission (CAI *4, with stool frequency and rectal bleeding subscores of *0*) in the course of the DB phase,

* Endoscopic Index (EI) and its change in the course of the DB phase,

* Percentage of patients in endoscopic remission (EI *3),

* Percentage of patients with endoscopic improvement (decrease *1 point in EI), and endoscopic deterioration (increase *1 point in EI),

* Number and percentage of patients in each level of change from baseline in the EI in the course of the DB phase,

* Histological Index (HI) and its change in the course of the DB phase,

* Percentage of patients in the categories histologic remission (HI * 1), mild (HI=2), moderate (HI=3), and severe (HI=4) activity at EOT/withdrawal visit,

* Percentage of patients with a histologic deterioration,

* Number and percentage of patients in each level of change from baseline in the HI in the course of the DB phase,

* Time in study,

* Time to clinical relapse,

* Number of stools per week,

* Number of bloody stools per week,

* Number of days with urgency per week,

* Patient*s quality of life,

* Work Productivity and Activity Impairment (WPAI),

* Number of days hospitalized,

* Patient*s Global Satisfaction.

Further secondary efficacy variables for the OLRI/OLE phase:

* Percentage of patients previously withdrawn from the DB-phase due to lack of efficacy and being back in clinical remission at Week 12 (LOCF) of the OLRI phase,

* Number and percentage of patients in each level of change from baseline (OLRI V1/OLE V1) in the mDAI subscores (1, 2, and 4) in the course of the OLRI/OLE phase,

* CAI and its change from baseline (OLRI V1/OLE V1) in the course of the OLRI/OLE phase,

* Percentage of patients in clinical remission defined as CAI *4 with *0* for *stools* and *blood in stools* subscores,

* Time in study,

* Time to clinical relapse or discontinuation,

* Patient*s quality of life,

* WPAI,

* Number of days hospitalized,

* Patient*s Global Satisfaction.

Further secondary efficacy variables for the OLI phase:

* 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 (LOCF),

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

* Total mDAI and its subscores and their changes in the course of the OLI phase,

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

* Percentage of patients with clinical remission (defined as CAI * 4, with stool frequency and rectal bleeding subscores of *0*) in the course of the OLI phase,

* Percentage of patients with clinical improvement (CAI) defined as a decrease of * 3 points compared to baseline in the course of the OLI phase,

* 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 [OLI V1]),

* 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 OLI phase,

* 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),

* Patient*s quality of life,

* Work Productivity and Activity Impairment (WPAI),

* Patient*s Global Satisfaction

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. 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. This mucus consists of a hydrated polymeric gel with
a thickness of 50-500 *m, with < 10% proteins, carbohydrates and lipids. 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. They
are largely responsible for establishing the hydrophobic surface and play a key role in the
barrier properties of the underlying tissue.

Study objective

Primary:
* To prove the superiority of a 48-weeks treatment with 3.2 g/day delayedrelease phosphatidylcholine (LT-02) versus placebo for the maintenance of remission in patients with ulcerative colitis (UC)
Secondary:
* To study safety and tolerability in the form of adverse events (AEs) and laboratory parameters,
* To assess patients* quality of life.
Open-label sub-study:
* To re-induce and/or maintain remission of UC in patients who prematurely dropped-out due to lack of efficacy or who completed the double-blind phase still being in remission.

Study design

This is a double-blind, double-dummy, randomized, placebo- and active controlled, multi-center, comparative, 48-week, confirmative Phase III clinical trial. The trial will be conducted with three arms in the form of a parallel group
comparison and will primarily serve to confirmatorily compare oral daily treatment with 3.2 g delayed-release phosphatidylcholine (LT-02) granules versus placebo for the maintenance of remission in patients with UC. The third arm, i.e. mesalamine, will serve as an internal control for assay sensitivity and
will only be compared to placebo and LT-02 in an exploratory manner. This trial has an optional interim analysis after approximately the first 200 consecutive enrolled patients (full analysis set [FAS]) have reached their primary endpoint, i.e., have either reached week 48 or discontinued early. The decision to perform the interim analysis will be solely based on recruitment. The study will be performed according to a 2-stage group-sequential adaptive design with possible sample size adjustment and treatment arm selection.
At the beginning of study enrolment, only patients being brought into remission during the double-blind (DB) or open-label (OL) phase of the trial PCG-2/UCA (EudraCT No. 2012-003702; acronym: PROTECT-1) will be allowed to be enrolled. Once enrolment of trial PCG-2/UCA is completed, the study will allow the enrollment of patients being brought into remission by OL-induction (OLI)

treatment with LT-02. These patients will be recruited according to the major in-and exclusion criteria of study PCG-2/UCA,
thus it will be ensured that the patient population in principle, i.e., patients not adequately responding to a
sufficient dose of mesalamine, will be the same.
Screening phase prior to open-label induction (OLI) (only available, if recruitment of study PCG-2 has been completed):
During 7 up to 10 days prior to OLI V1, 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).
OLI treatment phase (only available, if recruitment of study PCG-2 has been completed):
12-week OLI add-on treatment with 1.6 g LT-02 BID to underlying oral mesalamine treatment.
Screening phase prior to maintenance phase (for patients rolled-over from study PCG-2 or OLI phase):
Up to 10 days prior to baseline.
Double-blind (DB), double-dummy, randomized treatment for maintenance of remission:
Patients in remission of UC at the EOT visit of study PCG-2/UCA, or later at OLI V4, will be offered to continue in this maintenance trial. Results from the EOT visit of the PCG-2/UCA study or OLI V4 will be regarded as baseline values of this maintenance trial.
Patients will be randomized in a 2:1:1 ratio to receive a 48-week, double-blind, double-dummy treatment with either:
Group A: 1.6 g LT-02 twice daily (BID) AND mesalamine placebo granules three-times daily (TID),
Group B: LT-02 placebo BID AND mesalamine placebo granules TID, or
Group C: LT-02 placebo BID AND 500 mg mesalamine granules TID.
Randomization will be stratified by patient*s deep remission criterion, i.e., *modified Disease Activity Index (mDAI) score *1 with *0* points for rectal bleeding and stool frequency at baseline* (*yes* vs *no*).
Open-label (OL) sub-study (PCG-5/OLT):
Open-label re-induction (OLRI) phase: Patients prematurely discontinued from the DB-phase due to lack of efficacy will be offered an OL re-induction treatment with 1.6 g LT-02 BID for up to 12 weeks.
Open-label extension (OLE) phase: Patients completing the DB-phase without experiencing a relapse and those patients who have achieved a clinical response in the OLRI phase can receive OLE-treatment with LT-02 BID for up to 48 weeks (counting from the start of OL-treatment).
Follow-up phase:
Patients will be followed-up 4 weeks after their last treatment visit in the DB or

OL (OLI, OLRI, or OLE, respectively) phase, if not continuing in the study.

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

Inclusion criteria for DB maintenance phase:
1. Signed informed consent,
2. Men or women, 18 to 70 years of age,
3. Historically confirmed diagnosis of UC by endoscopy and histology,
4. Patients being in remission at baseline,
5. Negative pregnancy test in females of childbearing potential at baseline visit,
6. Women of child-bearing potential have to apply during the entire duration of the trial a highly effective method of birth control, which is defined as those which result in a low failure rate (i.e., less than 1% per year) when used constantly and correctly.

Exclusion criteria

Exclusion criteria for DB maintenance phase:
1. Crohn's disease, indeterminate colitis, ischemic colitis, radiation colitis, microscopic colitis (i.e., collagenous colitis and lymphocytic colitis), diverticular disease associated colitis,
2. Toxic megacolon or fulminant colitis,
3. Colon resection,
4. Malabsorption syndromes,
5. Celiac disease,
6. Bleeding hemorrhoids,
7. Other inflammatory or bleeding disorders of the colon and intestine, or diseases that may cause diarrhea or gastrointestinal bleeding,
8. History or presence of ischemic heart disease, myocardial infarction, peripheral arterial disease, ischemic stroke, or transient ischemic attack,
9. Any severe concomitant renal, endocrine, or psychiatric disorder, which in the opinion of the investigator might have an influence on the patient*s compliance or the interpretation of the results,
10. Any relevant known systemic disease (e.g., AIDS, active tuberculosis),
11. Severe co-morbidity substantially reducing life expectancy,
12. History of cancer in the last five years,
13. Abnormal hepatic function at the screening visit), liver cirrhosis,
14. Abnormal renal function at the screening visit,
15. Either HbA1c *6.5% (*48 mmol/mol) at baseline visit, OR HbA1c >5.6% (38 mmol/mol) AND fasting blood glucose *100 mg/dl (*5.6 mmol/l) at baseline visit,
16. Patients with known hypersensitivity to soy,
17. Known intolerance/hypersensitivity to Investigational Medicinal Product (IMP: LT-02 or mesalamine),
18. Treatment with steroids (oral, inhalative, or intravenous [IV]), cyclosporine or tacrolimus within last 4 weeks prior to randomization,
19. Treatment with methotrexate within last 6 weeks prior to randomization,

20. Treatment with TNF-alpha-antagonists, azathioprine, 6-mercaptopurine, or anti-integrin therapy within last 8 weeks prior to randomization,
21. Treatment with rectal mesalamine or corticosteroid formulations within last 2 weeks prior to randomization,
22. Treatment with other investigational drug within last 12 weeks prior to randomization except LT-02,
23. Concomitant treatment with coumarins (e.g., phenprocoumon),
24. Unwillingness to undergo endoscopy with biopsy sampling at end of treatment (EOT)/withdrawal visit of this study,
25. Clinical suspicion of addiction to alcohol or drugs,
26. Existing or intended pregnancy or breast-feeding,
27. Subjects deemed by the investigator to be unlikely to comply with the protocol requirements, instructions and study-related restrictions; e.g., uncooperative attitude, inability to return for follow-up visits, and improbability of completing the study,
28. Participation in another clinical trial within the last 30 days prior to baseline visit (except for the Phase III study PCG-2/UCA), simultaneous participation in another clinical trial, or previous participation in this trial and having received IMP.

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:	Prevention

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	28
Type:	Anticipated

Medical products/devices used

Product type:	Medicine

Brand name:	Lechitine
Generic name:	Phosphatidylcholine granules
Product type:	Medicine
Brand name:	Mesalazine
Generic name:	Mesalamine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	20-05-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Not approved Date:	01-06-2015
Application type:	First submission
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	EUCTR2013-001205-84-NL
CCMO	NL52721.091.15