



Clinical trial results:

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

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2013-001205-84 |
| Trial protocol | DE PL LT LV SK BE AT HU |
| Global end of trial date | 05 October 2018 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 02 January 2020 |
| First version publication date | 02 January 2020 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | PCG-4/UCR |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02280629 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Dr Falk Pharma GmbH |
| Sponsor organisation address | Leinenweberstrasse 5, Freiburg, Germany, 79108 |
| Public contact | Dep't of Research and Development, Dr Falk Pharma GmbH, +49 761-1514-0, |
| Scientific contact | Dep't of Research and Development, Dr Falk Pharma GmbH, +49 761-1514-0, |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 13 November 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 05 October 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 October 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Primary:

To prove the superiority of a 48-weeks treatment with 3.2 g/day delayed-release phosphatidylcholine (LT-02) versus placebo for the maintenance of remission in patients with ulcerative colitis (UC)

Protection of trial subjects:

Close supervision of subjects by implementing interim visits at week 4, 12, and then every 3 months, every 4 weeks during the open-label re-induction phase and at every 3 months during the open-label extension phase, to guarantee their safety and wellbeing.

Prior to recruitment of patients, all relevant documents of the clinical study were submitted and approved by the Independent Ethics Committees (IECs) responsible for the participating investigators. Written consent documents embodied the elements of informed consent as described in the Declaration of Helsinki, the ICH Guidelines for Good Clinical Practice (GCP) and were in accordance with all applicable laws and regulations. The informed consent form and patient information sheet described the planned and permitted uses, transfers and disclosures of the patient's personal data and personal health information for purposes of conducting the study. The informed consent form and the patient information sheet further explained the nature of the study, its objectives and potential risks and benefits as well as the date informed consent was given. Before being enrolled in the clinical trial, every patient was informed that participation in this trial was voluntary and that he/she could withdraw from the study at any time without giving a reason and without having to fear any loss in his/her medical care. The patient's consent was obtained in writing before the start of the study. By signing the informed consent, the patient declared that he/she was participating voluntarily and intended to follow the study protocol instructions and the instructions of the investigator and to answer the questions asked during the course of the trial.

Background therapy:

-

Evidence for comparator:

According to current consensus guidelines, mesalamine preparations are the mainstay of treatment for maintenance of remission in mild-to-moderate UC and have been shown to be superior to placebo.

| | |
|---|-----------------|
| Actual start date of recruitment | 01 October 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Poland: 29 |
| Country: Number of subjects enrolled | Slovakia: 1 |
| Country: Number of subjects enrolled | Austria: 1 |
| Country: Number of subjects enrolled | Germany: 69 |
| Country: Number of subjects enrolled | Hungary: 2 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Latvia: 4 |
| Country: Number of subjects enrolled | Lithuania: 3 |
| Country: Number of subjects enrolled | Russian Federation: 12 |
| Country: Number of subjects enrolled | Ukraine: 27 |
| Country: Number of subjects enrolled | Israel: 2 |
| Worldwide total number of subjects | 150 |
| EEA total number of subjects | 109 |

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 1 |
| Adults (18-64 years) | 144 |
| From 65 to 84 years | 5 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total number of 150 patients were randomized to LT-02 1.6 g two times daily, or Placebo, or Mesalamine 0.5 g 3 times daily. The initially planned patient-number could not be reached due to the premature termination of preceding induction trial PCG-2 (EudraCT # 2012-003702-27) causing a premature end of recruitment into PCG-4

Pre-assignment

Screening details:

Screening criteria:

1. Signed informed consent
2. Aged 18 to 70 years
3. Either in deep remission or remission at baseline, i.e. at the end of the preceding PCG-2 study.

Period 1

| | |
|------------------------------|--|
| Period 1 title | Double-blind phase (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Assessor |

Blinding implementation details:

The appearance and taste of sachets for oral administration were indistinguishable among the three treatment groups due to double-dummy-packaging. All patients took the same amount of sachets at the same times of the day.

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Group A |

Arm description:

1.6 g phosphatidylcholine in LT-02 BID

| | |
|--|---------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | LT-02 gastro-resistant granules |
| Investigational medicinal product code | Not applicable |
| Other name | |
| Pharmaceutical forms | Gastro-resistant granules |
| Routes of administration | Oral use |

Dosage and administration details:

Dosing: 1.6 g phosphatidylcholine in LT-02 sachets twice daily taken in the morning and in the evening, plus mesalamine placebo sachets taken in the morning, at lunchtime and in the evening.

Administration: LT-02 sachets: Ingest contents of one sachet 30 to 60 minutes before meal along with a glass of water. Alternatively, mix the content of the sachet with water, juice, or yoghurt; in this case, ingest the mixture immediately after preparation. Do not chew.

Mesalamine placebo sachets: The content of 1 sachet each has to be swallowed in the morning, at noon, and in the evening with plenty of water. Chewing of the study medication has to be avoided.

| | |
|------------------|---------|
| Arm title | Group B |
|------------------|---------|

Arm description:

Placebo

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|---|
| Investigational medicinal product name | LT-02 placebo gastro-resistant granules |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Gastro-resistant granules |
| Routes of administration | Oral use |

Dosage and administration details:

Dosing: LT-02 placebo sachets twice daily taken in the morning and in the evening, plus mesalamine placebo sachets taken in the morning, at lunchtime and in the evening.

Administration:

LT-02 placebo sachets: Ingest contents of one sachet 30 to 60 minutes before meal along with a glass of water. Alternatively, mix the content of the sachet with water, juice, or yoghurt; in this case, ingest the mixture immediately after preparation. Do not chew.

Mesalamine placebo sachets: The content of 1 sachet each has to be swallowed in the morning, at noon, and in the evening with plenty of water. Chewing of the study medication has to be avoided.

| | |
|--|--|
| Investigational medicinal product name | Mesalamine placebo gastro-resistant granules |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Gastro-resistant granules |
| Routes of administration | Oral use |

Dosage and administration details:

Dosing: LT-02 placebo sachets twice daily taken in the morning and in the evening, plus mesalamine placebo sachets taken in the morning, at lunchtime and in the evening.

Administration:

LT-02 placebo sachets: Ingest contents of one sachet 30 to 60 minutes before meal along with a glass of water. Alternatively, mix the content of the sachet with water, juice, or yoghurt; in this case, ingest the mixture immediately after preparation. Do not chew.

Mesalamine placebo sachets: The content of 1 sachet each has to be swallowed in the morning, at noon, and in the evening with plenty of water. Chewing of the study medication has to be avoided.

| | |
|------------------|---------|
| Arm title | Group C |
|------------------|---------|

Arm description:

Mesalamine 0,5 g TID

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | Mesalamine 0,5 g TID |
| Investigational medicinal product code | |
| Other name | Salofalk® 500 mg gastro-resistant prolonged-release granules |
| Pharmaceutical forms | Gastro-resistant granules |
| Routes of administration | Oral use |

Dosage and administration details:

Dosing: Mesalamine 0,5 g TID with mesalamine-sachets taken in the morning, at lunchtime and in the evening; plus LT-02 placebo sachets twice daily taken in the morning and in the evening.

Administration: Mesalamine sachets: The content of 1 sachet each has to be swallowed in the morning, at noon, and in the evening with plenty of water. Chewing of the study medication has to be avoided.

LT-02 placebo sachets: Ingest contents of one sachet 30 to 60 minutes before meal along with a glass of water. Alternatively, mix the content of the sachet with water, juice, or yoghurt; in this case, ingest the mixture immediately after preparation. Do not chew.

| Number of subjects in period 1 | Group A | Group B | Group C |
|---------------------------------------|---------|---------|---------|
| Started | 75 | 37 | 38 |
| Completed | 40 | 16 | 20 |
| Not completed | 35 | 21 | 18 |
| Lack of patient cooperation | - | - | 1 |
| Adverse event, non-fatal | 1 | - | - |
| Lack of patient's cooperation | 10 | - | - |
| unspecified | - | 2 | - |
| Lack of efficacy | 24 | 19 | 17 |

Baseline characteristics

Reporting groups

| | |
|--|---------|
| Reporting group title | Group A |
| Reporting group description: 1.6 g phosphatidylcholine in LT-02 BID | |
| Reporting group title | Group B |
| Reporting group description: Placebo | |
| Reporting group title | Group C |
| Reporting group description: Mesalamine 0,5 g TID | |

| Reporting group values | Group A | Group B | Group C |
|---|---------|---------|---------|
| Number of subjects | 75 | 37 | 38 |
| Age categorical | | | |
| Based on year of birth | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 1 |
| Adults (18-64 years) | 72 | 35 | 37 |
| From 65-84 years | 3 | 2 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Based on year of birth | | | |
| Units: years | | | |
| arithmetic mean | 39.5 | 42.0 | 40.7 |
| standard deviation | ± 11.28 | ± 13.04 | ± 11.66 |
| Gender categorical | | | |
| Assumed to be representative for overall patient population | | | |
| Units: Subjects | | | |
| Female | 32 | 13 | 18 |
| Male | 43 | 24 | 20 |

| Reporting group values | Total | | |
|---|-------|--|--|
| Number of subjects | 150 | | |
| Age categorical | | | |
| Based on year of birth | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |

| | | | |
|---|-----|--|--|
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 1 | | |
| Adults (18-64 years) | 144 | | |
| From 65-84 years | 5 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| Based on year of birth | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical | | | |
| Assumed to be representative for overall patient population | | | |
| Units: Subjects | | | |
| Female | 63 | | |
| Male | 87 | | |

Subject analysis sets

| | |
|-----------------------------------|---------------|
| Subject analysis set title | FAS |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| FAS: full analysis set | |

| | | | |
|---|---------|--|--|
| Reporting group values | FAS | | |
| Number of subjects | 150 | | |
| Age categorical | | | |
| Based on year of birth | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 1 | | |
| Adults (18-64 years) | 144 | | |
| From 65-84 years | 5 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| Based on year of birth | | | |
| Units: years | | | |
| arithmetic mean | 40.4 | | |
| standard deviation | ± 11.80 | | |
| Gender categorical | | | |
| Assumed to be representative for overall patient population | | | |
| Units: Subjects | | | |
| Female | 63 | | |
| Male | 87 | | |

End points

End points reporting groups

| | |
|--|---------------|
| Reporting group title | Group A |
| Reporting group description: 1.6 g phosphatidylcholine in LT-02 BID | |
| Reporting group title | Group B |
| Reporting group description: Placebo | |
| Reporting group title | Group C |
| Reporting group description: Mesalamine 0,5 g TID | |
| Subject analysis set title | FAS |
| Subject analysis set type | Full analysis |
| Subject analysis set description: FAS: full analysis set | |

Primary: Primary endpoint: Proportion of patients who are relapse-free and are not a treatment failure after 48 weeks

| | |
|---|--|
| End point title | Primary endpoint: Proportion of patients who are relapse-free and are not a treatment failure after 48 weeks |
| End point description: Proportion of patients who are relapse-free and are not a treatment failure after 48 weeks. Relapse defined as a rectal bleeding score of ≥ 1 and a mucosal appearance score of ≥ 2 as described in the mDAI score; 'treatment failure' defined as premature withdrawal (whatever the reason) during the double-blind phase. | |
| End point type | Primary |
| End point timeframe: Double-blind phase | |

| End point values | Group A | Group B | Group C | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 75 | 37 | 38 | |
| Units: Percentage | 75 | 37 | 38 | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Confirmative analysis: LT-02 1.6 g BID vs Placebo |
| Statistical analysis description: Confirmatory statistical analysis by comparison of LT-02 1.6 g BID vs Placebo | |
| Comparison groups | Group B v Group A |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 112 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | inverse normal method |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.5 |
| upper limit | 26.6 |

Secondary: Secondary: Change from Baseline of total mDAI

| | |
|---|---|
| End point title | Secondary: Change from Baseline of total mDAI |
| End point description: | |
| Change from Baseline of total mDAI at week 48 (LOCF). | |
| Analysis was only performed for LT-02 compared to placebo | |
| End point type | Secondary |
| End point timeframe: | |
| week 48/EOT | |

| End point values | Group A | Group B | Group C | |
|-------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 54 | 30 | 33 | |
| Units: Total mDAI score | | | | |
| least squares mean (standard error) | 2.17 (± 0.425) | 2.45 (± 0.570) | 2.64 (± 0.543) | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Analysis of change of total mDAI from Baseline |
| Statistical analysis description: | |
| Analysis of change from Baseline of total mDAI at week 48 (LOCF) | |
| Comparison groups | Group A v Group B |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3462 |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | -0.28 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.69 |
| upper limit | 1.13 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.711 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event were assessed from baseline to final visit

Adverse event reporting additional description:

Treatment emergent adverse events

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Group A |
|-----------------------|---------|

Reporting group description:

1.6 g phosphatidylcholine in LT-02 BID

| | |
|-----------------------|---------|
| Reporting group title | Group B |
|-----------------------|---------|

Reporting group description:

Placebo

| | |
|-----------------------|---------|
| Reporting group title | Group C |
|-----------------------|---------|

Reporting group description:

Mesalamine 0,5 g TID

| Serious adverse events | Group A | Group B | Group C |
|---|---|----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 75 (5.33%) | 0 / 37 (0.00%) | 1 / 38 (2.63%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | Additional description: Investigator term: Stroke left capsula interna | | |
| subjects affected / exposed | 1 / 75 (1.33%) | 0 / 37 (0.00%) | 0 / 38 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | Additional description: Investigator term: right-sided upper abdominal pain | | |
| subjects affected / exposed | 1 / 75 (1.33%) | 0 / 37 (0.00%) | 0 / 38 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | Additional description: Investigator term: Adhesive small bowel obstruction | | |

| | | | |
|---|---|----------------|----------------|
| subjects affected / exposed | 1 / 75 (1.33%) | 0 / 37 (0.00%) | 0 / 38 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | Additional description: Investigator term: acute pancreatitis | | |
| subjects affected / exposed | 0 / 75 (0.00%) | 0 / 37 (0.00%) | 1 / 38 (2.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholestasis | Additional description: Investigator term: hepatic cholestasis | | |
| subjects affected / exposed | 1 / 75 (1.33%) | 0 / 37 (0.00%) | 0 / 38 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Osteomyelitis | Additional description: Investigator term: Osteomyelitis left lower jaw | | |
| subjects affected / exposed | 1 / 75 (1.33%) | 0 / 37 (0.00%) | 0 / 38 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Group A | Group B | Group C |
|---|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 46 / 75 (61.33%) | 25 / 37 (67.57%) | 25 / 38 (65.79%) |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 4 / 75 (5.33%) | 2 / 37 (5.41%) | 0 / 38 (0.00%) |
| occurrences (all) | 4 | 2 | 0 |
| Colitis ulcerative | | | |
| subjects affected / exposed | 27 / 75 (36.00%) | 20 / 37 (54.05%) | 19 / 38 (50.00%) |
| occurrences (all) | 27 | 20 | 19 |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 75 (0.00%) | 3 / 37 (8.11%) | 0 / 38 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Infections and infestations | | | |

| | | | |
|---|---------------------|---------------------|----------------------|
| Nasopharyngitis subjects affected / exposed occurrences (all) | 7 / 75 (9.33%) 7 | 2 / 37 (5.41%) 2 | 4 / 38 (10.53%) 4 |
|---|---------------------|---------------------|----------------------|

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

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|--|
| Due to early termination of preceding induction trial PCG-2 (for futility), the recruitment into maintenance trial PCG-4 came to an end prematurely: Instead of the initially planned number of 400 patients, only 150 patients were randomised. |
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Notes: