



## 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
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#### 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:

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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:

<b>Subjects enrolled per age group</b>	
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
<b>Arm title</b>	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.

<b>Arm title</b>	Group B
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Arm description:

Placebo

Arm type	Placebo
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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.

<b>Arm title</b>	Group C
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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.

<b>Number of subjects in period 1</b>	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	

<b>Reporting group values</b>	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 $\geq 1$ and a mucosal appearance score of $\geq 2$ 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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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### Reporting groups

Reporting group title	Group A
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Reporting group description:

1.6 g phosphatidylcholine in LT-02 BID

Reporting group title	Group B
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Reporting group description:

Placebo

Reporting group title	Group C
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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
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## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### 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.

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: