



## Clinical trial results:

**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**

### Summary

EudraCT number	2012-003702-27
Trial protocol	DE BE AT CZ SK HU LT LV NL PL
Global end of trial date	16 December 2016

### Results information

Result version number	v1 (current)
This version publication date	09 March 2019
First version publication date	09 March 2019

### Trial information

#### Trial identification

Sponsor protocol code	PCG-2/UCA
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02142725
WHO universal trial number (UTN)	-
Other trial identifiers	PROTECT-1: Acronym

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, zentrale@drfalkpharma.de
Scientific contact	Dep't of Research and Development, Dr Falk Pharma GmbH, +49 761-1514-0, zentrale@drfalkpharma.de

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	28 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 December 2016
Global end of trial reached?	Yes
Global end of trial date	16 December 2016
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

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.

Protection of trial subjects:

Close supervision of subjects by implementing interim visits every 14 days and once more after 4 weeks during the 12 weeks double-blind phase and after 4 and after 8 weeks during the 12 weeks open-label phase, to guarantee their safety and wellbeing.

Prior to recruitment of patients, all relevant documents of the clinical study were submitted and proved 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: -

Actual start date of recruitment	02 July 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	Netherlands: 5
Country: Number of subjects enrolled	Poland: 73
Country: Number of subjects enrolled	Slovakia: 4
Country: Number of subjects enrolled	Austria: 12
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Czech Republic: 7

Country: Number of subjects enrolled	Germany: 238
Country: Number of subjects enrolled	Hungary: 17
Country: Number of subjects enrolled	Latvia: 11
Country: Number of subjects enrolled	Lithuania: 8
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	Russian Federation: 30
Country: Number of subjects enrolled	Ukraine: 49
Worldwide total number of subjects	465
EEA total number of subjects	378

Notes:

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### **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)	443
From 65 to 84 years	21
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

A total of 468 patients were randomised to treatment with LT-02 0.8 g four times daily (QID), LT-02 1.6 g two times daily (BID), or placebo. Of these, 465 patients received at least one dose of study medication and had at least one follow-up value for the safety variables to be analysed.

### Pre-assignment

Screening details:

Screening details: Screening criteria:

1. Signed informed consent
2. Aged 18 to 70 years
3. Mesalamine (5-ASA) refractory disease defined as a total mDAI Score of  $\geq 4$  and  $\leq 10$

### 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, Carer, Assessor

Blinding implementation details:

The appearance and taste of sachets for oral administration were indistinguishable among the three treatment groups due to the double-dummy-packaging. All patients took the same amount of sachets at the same times of the day (2 in the morning, 1 at lunch-time, 1 in the afternoon, 2 in the evening).

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Group A

Arm description:

0.8 g PC in LT-02 QID (four times daily)

Arm type	Experimental
Investigational medicinal product name	phosphatidylcholine (LT-02, gastro-resistant granules)
Investigational medicinal product code	
Other name	phosphatidylcholine
Pharmaceutical forms	Gastro-resistant granules
Routes of administration	Oral use

Dosage and administration details:

Dosing: 0.8 g phosphatidylcholine in LT-02 four times daily, with placebo sachets taken with morning and evening doses as part of double-dummy packaging.

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

1.6 g PC in LT-02 BID (twice daily)

Arm type	Experimental
Investigational medicinal product name	phosphatidylcholine (LT-02, gastro-resistant granules)
Investigational medicinal product code	
Other name	phosphatidylcholine
Pharmaceutical forms	Gastro-resistant granules
Routes of administration	Oral use

Dosage and administration details:

Dosing: 1.6 g PC in LT-02 twice daily, with placebo sachets taken during lunchtime and afternoon doses,

as part of double-dummy packaging.

Administration: 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>Arm title</b>	Group C
Arm description: Placebo QID (four times daily)	
Arm type	Placebo
Investigational medicinal product name	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: Placebo sachets taken four times daily (QID).

Administration: 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	155	155	155
Completed	109	112	109
Not completed	46	43	46
Lack of patient cooperation	7	4	3
Adverse event, non-fatal	-	1	-
Other (unspecified)	-	10	-
unspecified	14	-	10
Lack of efficacy	25	28	33

## Baseline characteristics

### Reporting groups

Reporting group title	Double-blind phase
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Reporting group description: -

Reporting group values	Double-blind phase	Total	
Number of subjects	465	465	
Age categorical			
Based on year of birth			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	1	1	
Adults (18-64 years)	443	443	
From 65-84 years	21	21	
85 years and over	0	0	
Age continuous			
based on year of birth			
Units: years			
arithmetic mean	39.9		
standard deviation	± 12.83	-	
Gender categorical			
assumed representative for overall patient population			
Units: Subjects			
Female	200	200	
Male	265	265	

## End points

### End points reporting groups

Reporting group title	Group A
Reporting group description: 0.8 g PC in LT-02 QID (four times daily)	
Reporting group title	Group B
Reporting group description: 1.6 g PC in LT-02 BID (twice daily)	
Reporting group title	Group C
Reporting group description: Placebo QID (four times daily)	
Subject analysis set title	Confirmative analysis
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis set (FAS) defined according to the intention-to-treat (ITT) principle was the primary population for analysis and included all randomized patients (as randomized) who received at least one dose of an IMP and who had UC at baseline or in whom UC could not definitely be excluded. The intention-to-treat principle was preserved despite the exclusion of patients who took no IMP, as the decision of whether or not to begin treatment could not be influenced by knowledge of the assigned treatment.	

### Primary: Proportion of patients in Deep clinical remission at week 12 (LOCF)

End point title	Proportion of patients in Deep clinical remission at week 12 (LOCF)
End point description: Deep clinical remission was defined as a modified DAI Score $\leq 1$ with '0' points for rectal bleeding and stool frequency, and $\geq 1$ point reduction from baseline in the mucosal appearance score, at week 12 (LOCF)	
End point type	Primary
End point timeframe: 12 weeks (LOCF)	

End point values	Group A	Group B	Group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	155	155	155	
Units: Patients	15	22	21	

### Statistical analyses

Statistical analysis title	Confirmative analysis: 0.8 g QID vs placebo
Statistical analysis description: Confirmatory statistical analysis by comparison of 0.8 g QID against placebo	
Comparison groups	Group A v Group C

Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority <sup>[1]</sup>
P-value	= 0.2875 <sup>[2]</sup>
Method	Normal approximation test
Parameter estimate	Risk difference (RD)
Point estimate	-0.039
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.032

Notes:

[1] - closed testing procedure with Simes intersection test ( $\alpha = 0.025$ , one-sided)

[2] - Testing of  $H_0$  ( $n_{Pla} > n_{0.8 \text{ g QID}}$ ) by means of the normal approximation test for rates ( $\alpha = 0.025$  one-sided). A closed testing procedure with the Simes intersection test was used to adjust for multiplicity testing of both verum groups versus placebo.

<b>Statistical analysis title</b>	Confirmative analysis: 1.6 g BID vs placebo
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Statistical analysis description:

Confirmatory statistical analysis by comparison of 1.6 g BID against placebo.

Comparison groups	Group B v Group C
Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority <sup>[3]</sup>
P-value	= 0.8695 <sup>[4]</sup>
Method	Normal approximation test
Parameter estimate	Risk difference (RD)
Point estimate	0.006
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.083

Notes:

[3] - Closed testing procedure with Simes intersection test ( $\alpha = 0.025$  one-sided)

[4] - Testing of  $H_0$  ( $n_{Pla} > n_{1.6 \text{ g BID}}$ ) by means of the normal approximation test for rates ( $\alpha = 0.025$  one-sided). A closed testing procedure with the Simes intersection test was used to adjust for multiplicity testing of both verum groups versus placebo.

### **Secondary: Proportion of patients in Remission at Week 12 (LOCF)**

End point title	Proportion of patients in Remission at Week 12 (LOCF)
End point description:	
Remission: defined as total mDAI score $\leq 2$ with no sub-score $> 1$	
End point type	Secondary
End point timeframe:	
12 weeks (LOCF)	



End point values	Group A	Group B	Group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	155	155	155	
Units: Patients	21	16	15	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of patients with Clinical Improvement in mDAI at week 12 (LOCF)

End point title	Proportion of patients with Clinical Improvement in mDAI at week 12 (LOCF)
End point description: Clinical Improvement defined as total mDAI score decrease of at least 3 points	
End point type	Secondary
End point timeframe: 12 weeks (LOCF)	

End point values	Group A	Group B	Group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	155	155	155	
Units: Patients	28	38	33	

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events 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:

LT-02 0.8 g QID

Reporting group title	Group B
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Reporting group description:

LT-02 1.6 g BID

Reporting group title	Group C
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Reporting group description:

Placebo

Serious adverse events	Group A	Group B	Group C
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 155 (3.23%)	8 / 155 (5.16%)	4 / 155 (2.58%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Surgical and medical procedures			
Cartilage graft			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	1 / 155 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Unintended pregnancy			
subjects affected / exposed	1 / 155 (0.65%)	1 / 155 (0.65%)	0 / 155 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 155 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pseudopolyp			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	1 / 155 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Chorioretinopathy			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	1 / 155 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Anal fistula			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	1 / 155 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ulcerative			
subjects affected / exposed	3 / 155 (1.94%)	3 / 155 (1.94%)	1 / 155 (0.65%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctalgia			
subjects affected / exposed	1 / 155 (0.65%)	0 / 155 (0.00%)	0 / 155 (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
Vomiting			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 155 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Uterine scar			

subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 155 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Infections and infestations</b>			
Abscess limb			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 155 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Campylobacter gastroenteritis</b>			
subjects affected / exposed	1 / 155 (0.65%)	0 / 155 (0.00%)	0 / 155 (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 %

<b>Non-serious adverse events</b>	Group A	Group B	Group C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	80 / 155 (51.61%)	83 / 155 (53.55%)	82 / 155 (52.90%)
<b>Nervous system disorders</b>			
Headache			
subjects affected / exposed	12 / 155 (7.74%)	13 / 155 (8.39%)	22 / 155 (14.19%)
occurrences (all)	12	13	22
<b>Gastrointestinal disorders</b>			
Colitis ulcerative			
subjects affected / exposed	21 / 155 (13.55%)	18 / 155 (11.61%)	21 / 155 (13.55%)
occurrences (all)	21	18	21
Nausea			
subjects affected / exposed	8 / 155 (5.16%)	3 / 155 (1.94%)	4 / 155 (2.58%)
occurrences (all)	8	3	4
<b>Infections and infestations</b>			
Nasopharyngitis			
subjects affected / exposed	12 / 155 (7.74%)	10 / 155 (6.45%)	14 / 155 (9.03%)
occurrences (all)	12	10	14

## 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.

Per recommendation from the IDMC the study was early terminated due to futility
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Notes: