

**Clinical trial results:****Double-blind, randomized, placebo-controlled, phase II dose-finding study comparing different doses of norursodeoxycholic acid capsules with placebo in the treatment of primary sclerosing cholangitis****Summary**

EudraCT number	2011-002754-31
Trial protocol	DE AT NL LT NO SE GB ES FI HU DK BE
Global end of trial date	22 October 2015

Results information

Result version number	v1 (current)
This version publication date	07 January 2017
First version publication date	07 January 2017

Trial information**Trial identification**

Sponsor protocol code	NUC-3/PSC
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Dr. Falk Pharma GmbH
Sponsor organisation address	Leinenweberstrasse 5, Freiburg, Germany, D-79108
Public contact	Dr. Markus Proels, Dr. Falk Pharma GmbH, +49 7611514-0, zentrale@drfalkpharma.de
Scientific contact	Dr. Markus Proels, Dr. Falk Pharma GmbH, +49 7611514-0, 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	16 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 October 2015
Global end of trial reached?	Yes
Global end of trial date	22 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of three doses of norUDCA vs. placebo for the treatment of PSC;

To identify efficacious and safe norUDCA dose(s) for the treatment of PSC for further evaluation in phase III

Protection of trial subjects:

Close supervision of subjects by implementing interim visits every 14 days 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:

None

Evidence for comparator:

Not applicable

Actual start date of recruitment	04 January 2013
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: 9
Country: Number of subjects enrolled	Norway: 7
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Sweden: 15
Country: Number of subjects enrolled	United Kingdom: 23
Country: Number of subjects enrolled	Austria: 16

Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	Finland: 8
Country: Number of subjects enrolled	Germany: 54
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	Lithuania: 2
Worldwide total number of subjects	159
EEA total number of subjects	159

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)	0
Adults (18-64 years)	153
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 222 patients were screened. 159 patients were randomized and received study drug.

Pre-assignment

Screening details:

Screening Criteria: 1. Signed Informed Consent 2. Aged 18 to 80 years. 3. Verified Primary sclerosing cholangitis .

Period 1

Period 1 title	Treatment Phase (overall trial) (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:

Conducted with the double-blind design.

Arms

Are arms mutually exclusive?	Yes
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Arm title	Group A
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Arm description:

2 x 250 mg Norursodeoxycholic acid + 4 x placebo capsules once daily (OD)

Arm type	Experimental
Investigational medicinal product name	Norursodeoxycholic acid 250 mg
Investigational medicinal product code	Not applicable
Other name	Not applicable
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

2 x 250 mg Norursodeoxycholic acid capsules + 4 placebo capsules once daily (OD)

Arm title	Group B
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Arm description:

4 x 250 mg Norursodeoxycholic acid capsules + 2 placebo capsules once daily (OD)

Arm type	Experimental
Investigational medicinal product name	Norursodeoxycholic acid 250 mg
Investigational medicinal product code	Not applicabe
Other name	Not applicable
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

4 x 250 mg Norursodeoxycholic acid capsules + 2 placebo capsules once daily (OD)

Arm title	Group C
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Arm description:

6 x 250 mg Norursodeoxycholic acid capsules once daily (OD)

Arm type	Experimental
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Investigational medicinal product name	Norursodeoxycholic acid 250 mg
Investigational medicinal product code	Not applicable
Other name	Not applicable
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

6 x 250 mg Norursodeoxycholic acid capsules once daily (OD)

Arm title	Group D
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Arm description:

6 x placebo capsules once daily (OD)

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	Not applicable
Other name	Not applicable
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

6 x Placebo capsules once daily (OD)

Number of subjects in period 1	Group A	Group B	Group C
Started	39	41	39
Completed	39	41	39

Number of subjects in period 1	Group D
Started	40
Completed	40

Baseline characteristics

Reporting groups

Reporting group title	Treatment Phase (overall trial)
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Reporting group description:

A total of 222 patients were screened. 159 patients were randomized and received study drug.

Reporting group values	Treatment Phase (overall trial)	Total	
Number of subjects	159	159	
Age categorical			
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)	0	0	
Adults (18-64 years)	153	153	
From 65-84 years	6	6	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	50	50	
Male	109	109	

End points

End points reporting groups

Reporting group title	Group A
Reporting group description:	2 x 250 mg Norursodeoxycholic acid + 4 x placebo capsules once daily (OD)
Reporting group title	Group B
Reporting group description:	4 x 250 mg Norursodeoxycholic acid capsules + 2 placebo capsules once daily (OD)
Reporting group title	Group C
Reporting group description:	6 x 250 mg Norursodeoxycholic acid capsules once daily (OD)
Reporting group title	Group D
Reporting group description:	6 x placebo capsules once daily (OD)

Primary: Relative change in serum alkaline phosphatase

End point title	Relative change in serum alkaline phosphatase
End point description:	Relative change (%) in serum alkaline phosphatase between baseline visit and EOT visit (LOCF)
End point type	Primary
End point timeframe:	Baseline Visit to EOT visit (LOCF)

End point values	Group A	Group B	Group C	Group D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	41	39	40
Units: percent				
number (not applicable)	-12.3	-17.3	-26	1.2

Statistical analyses

Statistical analysis title	Mean relative change in serum ALP: group A vs D
Statistical analysis description:	Each of the active treatment groups was compared to the placebo group. In order to adjust for multiplicity a closed testing procedure using Simes intersection tests was applied. As the distribution of relative changes (%) was expected to be skewed, one-sided Wilcoxon rank sum tests were used to test the hypotheses.
Comparison groups	Group A v Group D

Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0029 ^[1]
Method	one-sided Wilcoxon rank sum test
Parameter estimate	Mean difference (final values)
Confidence interval	
level	Other: 97.5 %
sides	1-sided

Notes:

[1] - If the global hypothesis could be rejected, then the pairwise intersection hypotheses $H_0(i) \cap H_0(j)$, $i, j = 1, 2, 3$, were tested and rejected if any $p(j) \leq j \times \alpha / 2$, i.e., if $p(1) \leq \alpha/2$ or $p(2) \leq \alpha = 0.025$.

Statistical analysis title	Mean relative change in serum ALP: group B vs D
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Statistical analysis description:

Each of the active treatment groups was compared to the placebo group. In order to adjust for multiplicity a closed testing procedure using Simes intersection tests was applied. As the distribution of relative changes (%) was expected to be skewed, one-sided Wilcoxon rank sum tests were used to test the hypotheses.

Comparison groups	Group B v Group D
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 ^[2]
Method	one-sided Wilcoxon rank sum test
Parameter estimate	Mean difference (final values)
Confidence interval	
level	Other: 97.5 %
sides	1-sided

Notes:

[2] - If the global hypothesis could be rejected, then the pairwise intersection hypotheses $H_0(i) \cap H_0(j)$, $i, j = 1, 2, 3$, were tested and rejected if any $p(j) \leq j \times \alpha / 2$, i.e., if $p(1) \leq \alpha/2$ or $p(2) \leq \alpha = 0.025$.

Statistical analysis title	Mean relative change in serum ALP: group C vs D
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Statistical analysis description:

Each of the active treatment groups was compared to the placebo group. In order to adjust for multiplicity a closed testing procedure using Simes intersection tests was applied. As the distribution of relative changes (%) was expected to be skewed, one-sided Wilcoxon rank sum tests were used to test the hypotheses.

Comparison groups	Group C v Group D
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[3]
Method	one-sided Wilcoxon rank sum test
Parameter estimate	Mean difference (final values)
Confidence interval	
level	Other: 97.5 %
sides	1-sided

Notes:

[3] - If the global hypothesis could be rejected, then the pairwise intersection hypotheses $H_0(i) \cap H_0(j)$, $i, j = 1, 2, 3$, were tested and rejected if any $p(j) \leq j \times \alpha / 2$, i.e., if $p(1) \leq \alpha/2$ or $p(2) \leq \alpha = 0.025$.

Secondary: Relative change in ALT

End point title	Relative change in ALT
End point description: Relative change in ALT (%) from Baseline to EOT (LOCF)	
End point type	Secondary
End point timeframe: Baseline visit to EOT visit (LOCF)	

End point values	Group A	Group B	Group C	Group D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	41	39	40
Units: percent				
number (not applicable)				
Relative change in ALT	-6.2	-21.9	-33.1	7.8

Statistical analyses

No statistical analyses for this end point

Secondary: Relative change in Gamma-GT

End point title	Relative change in Gamma-GT
End point description: Relative change in Gamma-GT (%) from Baseline to EOT (LOCF).	
End point type	Secondary
End point timeframe: Baseline vsist to EOT (LOCF):	

End point values	Group A	Group B	Group C	Group D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	41	39	40
Units: percent				
number (not applicable)				
Relative change in GGT	-8.9	-26.1	-33.9	0.3

Statistical analyses

No statistical analyses for this end point

Secondary: Relative change in AST

End point title	Relative change in AST
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End point description:	
Relative change in AST (%) from Baseline to EOT (LOCF)	
End point type	Secondary
End point timeframe:	
Baseline visit to EOT visit (LOCF):	

End point values	Group A	Group B	Group C	Group D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	41	39	40
Units: percent				
number (not applicable)				
Relative change in AST	9.6	-15.8	-20.5	8.1

Statistical analyses

No statistical analyses for this end point

Secondary: Relative change in total bilirubin

End point title	Relative change in total bilirubin
End point description:	
Relative change in total Bilirubin (%) from Baseline to EOT (LOCF).	
End point type	Secondary
End point timeframe:	
Baseline visit to EOT visit (LOCF).	

End point values	Group A	Group B	Group C	Group D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	41	39	40
Units: percent				
number (not applicable)				
Relative change in total Bilirubin	10.8	11.1	2.5	23.2

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were assessed at Baseline, all interim Visits (Weeks 2, 4, 6, 8 and 10) and at the Final Visit(Week 12), thus every 2 weeks.

Adverse event reporting additional description:

Treatment-Emergent Adverse Event

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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Reporting groups

Reporting group title	Group A
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Reporting group description:

2 x 250 mg Norursodeoycholic acid + 4 x placebo capsules once daily (OD)

Reporting group title	Group B
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Reporting group description:

4 x 250 mg Norursodeoxycholic acid capsules + 2 placebo capsules once daily (OD)

Reporting group title	Group C
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Reporting group description:

6 x 250 mg Norursodeoxycholic acid capsules once daily (OD)

Reporting group title	Group D
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Reporting group description:

6 x placebo capsules once daily (OD)

Serious adverse events	Group A	Group B	Group C
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 39 (7.69%)	1 / 41 (2.44%)	1 / 39 (2.56%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	0 / 39 (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
Eye disorders			
Ocular icterus			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Disease progression			
subjects affected / exposed	1 / 39 (2.56%)	1 / 41 (2.44%)	0 / 39 (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
Endoscopic retrograde cholangiopancreatography			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis acute			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Meniscus removal			
subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	0 / 39 (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

Serious adverse events	Group D		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 40 (7.50%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Ocular icterus			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Disease progression			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endoscopic retrograde cholangiopancreatography			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholangitis acute			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Meniscus removal			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	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	23 / 39 (58.97%)	30 / 41 (73.17%)	26 / 39 (66.67%)
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 39 (5.13%)	1 / 41 (2.44%)	7 / 39 (17.95%)
occurrences (all)	4	1	7
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 39 (5.13%)	2 / 41 (4.88%)	5 / 39 (12.82%)
occurrences (all)	2	2	5
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	4 / 41 (9.76%) 4	1 / 39 (2.56%) 1
Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	3 / 41 (7.32%) 3	3 / 39 (7.69%) 3
Diarrhoea subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	1 / 41 (2.44%) 1	3 / 39 (7.69%) 3
Nausea subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	2 / 41 (4.88%) 2	2 / 39 (5.13%) 2
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 4	4 / 41 (9.76%) 5	6 / 39 (15.38%) 11
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	0 / 41 (0.00%) 0	3 / 39 (7.69%) 3
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	6 / 39 (15.38%) 7	9 / 41 (21.95%) 11	8 / 39 (20.51%) 10

Non-serious adverse events	Group D		
Total subjects affected by non-serious adverse events subjects affected / exposed	32 / 40 (80.00%)		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 4		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 5		
Gastrointestinal disorders			

Abdominal pain subjects affected / exposed occurrences (all)	5 / 40 (12.50%) 7		
Abdominal pain upper subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3		
Diarrhoea subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 4		
Nausea subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 6		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 4		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	7 / 40 (17.50%) 8		

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

None reported