

**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 non-alcoholic fatty liver disease (NAFLD)****Summary**

EudraCT number	2013-004605-38
Trial protocol	DE AT
Global end of trial date	20 September 2016

Results information

Result version number	v2 (current)
This version publication date	04 October 2019
First version publication date	26 January 2019
Version creation reason	• Changes to summary attachments full publication attached
Summary attachment (see zip file)	Traussnigg-Lancet Gastro and Hepatol-2019 (Traussnigg-Lancet Gastro and Hepatol-2019.pdf)

Trial information**Trial identification**

Sponsor protocol code	NUC-4/NAS
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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, 79108
Public contact	Dept. of Clin. Res. & Development, Dr. Falk Pharma GmbH, 0049 76115140, zentrale@drfalkpharma.de
Scientific contact	Dept. of Clin. Res. & Development, Dr. Falk Pharma GmbH, 0049 76115140, 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 February 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 September 2016
Global end of trial reached?	Yes
Global end of trial date	20 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of two doses of norursodeoxycholic acid (norUDCA) vs. placebo for the treatment of NAFLD with or without diabetes mellitus type 2

Protection of trial subjects:

Close supervision of subjects by implementing interim visits every 14 days during the first 4 weeks of treatment and every 4 weeks up to the Follow- Visit at Week 16 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: -

Actual start date of recruitment	30 March 2015
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	Austria: 37
Country: Number of subjects enrolled	Germany: 161
Worldwide total number of subjects	198
EEA total number of subjects	198

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)	186
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 200 patients were enrolled into the study in Austria and Germany from March 2015 to September 2016.

Pre-assignment

Screening details:

Screening Criteria: 1. Signed Informed Consent 2. Age \geq 18 years 3. NAFLD 4. ALT $>$ 0.8 ULN. In total, 282 patients were screened. Thereof 200 patients were randomised and 198 patients received at least one dose of study medication and were included in the safety set and full analysis set (FAS) .

Period 1

Period 1 title	Treatment 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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Norursodeoxycholic acid 1500 mg once daily (6 norUDCA capsules à 250 mg)

Arm type	Experimental
Investigational medicinal product name	Norursodeoxycholic acid 1500 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Norursodeoxycholic acid 1500 mg once daily (6 norUDCA capsules à 250 mg)

Arm title	Arm B
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Arm description:

Norursodeoxycholic acid 500 mg once daily (2 norUDCA capsules à 250 mg and 4 placebo capsules à 250 mg)

Arm type	Experimental
Investigational medicinal product name	Norursodeoxycholic acid 500 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Norursodeoxycholic acid 500 mg once daily (2 norUDCA capsules à 250 mg and 4 placebo capsules à 250 mg)

Arm title	Arm C
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Arm description:

6 placebo capsules à 250 mg once daily

Arm type	Placebo
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Investigational medicinal product name	6 placebo capsules à 250 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

6 placebo capsules à 250 mg once daily

Number of subjects in period 1	Arm A	Arm B	Arm C
Started	67	67	64
Completed	60	64	61
Not completed	7	3	3
other reasons	2	-	-
Adverse event, non-fatal	5	2	2
patient wish	-	1	1

Baseline characteristics

Reporting groups

Reporting group title	Treatment Phase (overall period)
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Reporting group description: -

Reporting group values	Treatment Phase (overall period)	Total	
Number of subjects	198	198	
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)	186	186	
From 65-84 years	12	12	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	47.5		
full range (min-max)	19 to 73	-	
Gender categorical			
Units: Subjects			
Female	75	75	
Male	123	123	

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description: Norursodeoxycholic acid 1500 mg once daily (6 norUDCA capsules à 250 mg)	
Reporting group title	Arm B
Reporting group description: Norursodeoxycholic acid 500 mg once daily (2 norUDCA capsules à 250 mg and 4 placebo capsules à 250 mg)	
Reporting group title	Arm C
Reporting group description: 6 placebo capsules à 250 mg once daily	

Primary: Relative change in ALT

End point title	Relative change in ALT
End point description: Relative change (%) in ALT between V2 and V6-LOCF	
End point type	Primary
End point timeframe: Between V2 (Baseline) and V6-LOCF	

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	67	64	
Units: percent				
arithmetic mean (standard deviation)	-17.4 (± 26.1)	-4.2 (± 37.5)	10.4 (± 51.0)	

Statistical analyses

Statistical analysis title	normal approximation test for comparing two rates
Statistical analysis description: the inverse normal method of combining the p-values of the normal approximation test for comparing two rates.	
Comparison groups	Arm A v Arm B v Arm C
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	< 0.0001 ^[2]
Method	approx.-test for comparing two rates

Notes:

[1] - For estimating the treatment effect, the difference between the mean relative ALT change (%) from baseline in the respective treatment group and in the placebo group is provided together with the corresponding two-sided 95% repeated confidence interval (RCI).

[2] - Difference between means of Arm A (N1500) and Arm C (Placebo) was -27.8 (overall p-value < 0.0001; 95%-RCI [-34.7,-14.4]).

Difference between means of Arm B (N500) and Arm C (Placebo) was -14.6 (overall p-value = 0.0905; 95%-RCI [-20.7, 3.59]).

Secondary: Number of patients with ALT ≤ 0.8 ULN at V6-LOCF

End point title	Number of patients with ALT ≤ 0.8 ULN at V6-LOCF
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End point description:

End point type	Secondary
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End point timeframe:

proportion of patients with ALT ≤ 0.8 ULN at V6-LOCF

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	61	58	
Units: patients				
number (not applicable)	10	9	3	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were assessed at all interim visits (Week 2, 4, 8) to final visit of individual patient or Week 12 respectively. There was a 4-week follow-up after EOT.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Arm A
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Reporting group description:

Norursodeoxycholic acid 1500 mg once daily (6 norUDCA capsules à 250 mg)

Reporting group title	Arm B
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Reporting group description:

Norursodeoxycholic acid 500 mg once daily (2 norUDCA capsules à 250 mg and 4 placebo capsules à 250 mg)

Reporting group title	Arm C
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Reporting group description:

6 placebo capsules à 250 mg once daily

Serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 67 (1.49%)	2 / 67 (2.99%)	3 / 64 (4.69%)
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)			
Bladder cancer recurrent			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Joint dislocation			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Ventricular extrasystoles			

subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	0 / 64 (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
Reproductive system and breast disorders			
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	0 / 64 (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
Infections and infestations			
Abscess neck			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	0 / 64 (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
Erysipelas			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 67 (68.66%)	44 / 67 (65.67%)	45 / 64 (70.31%)
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 67 (14.93%)	6 / 67 (8.96%)	3 / 64 (4.69%)
occurrences (all)	11	6	3
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 67 (0.00%)	5 / 67 (7.46%)	4 / 64 (6.25%)
occurrences (all)	0	5	4
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 67 (10.45%)	5 / 67 (7.46%)	6 / 64 (9.38%)
occurrences (all)	7	5	7

Nausea subjects affected / exposed occurrences (all)	6 / 67 (8.96%) 7	1 / 67 (1.49%) 2	3 / 64 (4.69%) 4
Abdominal pain upper subjects affected / exposed occurrences (all)	3 / 67 (4.48%) 3	6 / 67 (8.96%) 7	2 / 64 (3.13%) 2
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	4 / 67 (5.97%) 4	0 / 67 (0.00%) 0	0 / 64 (0.00%) 0
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	7 / 67 (10.45%) 8	6 / 67 (8.96%) 7	6 / 64 (9.38%) 6

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