



## 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          | v1              |
| This version publication date  | 26 January 2019 |
| First version publication date | 26 January 2019 |

### Trial information

#### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | NUC-4/NAS |
|-----------------------|-----------|

#### 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:

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**Results analysis stage**

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|                                                      |                   |
|------------------------------------------------------|-------------------|
| 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:

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**General information about the trial**

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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:

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**Population of trial subjects**

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**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:

| <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)                 | 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   |
| <b>Arm title</b>             | 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)

|                  |       |
|------------------|-------|
| <b>Arm title</b> | Arm B |
|------------------|-------|

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)

|                  |       |
|------------------|-------|
| <b>Arm title</b> | Arm C |
|------------------|-------|

Arm description:

6 placebo capsules à 250 mg once daily

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

|                                        |                             |
|----------------------------------------|-----------------------------|
| 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

| <b>Number of subjects in period 1</b> | 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) |
|-----------------------|----------------------------------|

Reporting group description: -

| Reporting group values                                | Treatment Phase<br>(overall period) | Total |  |
|-------------------------------------------------------|-------------------------------------|-------|--|
| Number of subjects                                    | 198                                 | 198   |  |
| Age categorical                                       |                                     |       |  |
| Units: Subjects                                       |                                     |       |  |
| In utero                                              | 0                                   | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0                                   | 0     |  |
| Newborns (0-27 days)                                  | 0                                   | 0     |  |
| Infants and toddlers (28 days-23<br>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:<br>Norursodeoxycholic acid 1500 mg once daily (6 norUDCA capsules à 250 mg)                                |       |
| Reporting group title                                                                                                                   | Arm B |
| Reporting group description:<br>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:<br>6 placebo capsules à 250 mg once daily                                                                  |       |

### Primary: Relative change in ALT

|                                                                             |                        |
|-----------------------------------------------------------------------------|------------------------|
| End point title                                                             | Relative change in ALT |
| End point description:<br>Relative change (%) in ALT between V2 and V6-LOCF |                        |
| End point type                                                              | Primary                |
| End point timeframe:<br>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:<br>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 <sup>[1]</sup>                        |
| P-value                                                                                                                                            | < 0.0001 <sup>[2]</sup>                           |
| 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]).

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

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

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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| 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               |  |

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**Statistical analyses**

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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 |
|-----------------|------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

### 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

| 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          |
| <b>Reproductive system and breast disorders</b> |                |                |                |
| 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          |
| <b>Infections and infestations</b>              |                |                |                |
| 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 %

| <b>Non-serious adverse events</b>                           | 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%) |
| <b>Nervous system disorders</b>                             |                  |                  |                  |
| Headache                                                    |                  |                  |                  |
| subjects affected / exposed                                 | 10 / 67 (14.93%) | 6 / 67 (8.96%)   | 3 / 64 (4.69%)   |
| occurrences (all)                                           | 11               | 6                | 3                |
| <b>General disorders and administration site conditions</b> |                  |                  |                  |
| Fatigue                                                     |                  |                  |                  |
| subjects affected / exposed                                 | 0 / 67 (0.00%)   | 5 / 67 (7.46%)   | 4 / 64 (6.25%)   |
| occurrences (all)                                           | 0                | 5                | 4                |
| <b>Gastrointestinal disorders</b>                           |                  |                  |                  |
| Diarrhoea                                                   |                  |                  |                  |
| subjects affected / exposed                                 | 7 / 67 (10.45%)  | 5 / 67 (7.46%)   | 6 / 64 (9.38%)   |
| occurrences (all)                                           | 7                | 5                | 7                |

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

## **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**

None reported