



## Clinical trial results:

### High dose antioxidant treatment of patients with cystic fibrosis evaluated by measuring desmosine/isodesmosine in urine

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2016-000354-35 |
| Trial protocol           | DK             |
| Global end of trial date | 01 March 2017  |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 29 October 2017 |
| First version publication date | 29 October 2017 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | 2016-01 |
|-----------------------|---------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Aarhus University Hospital   |
| Sponsor organisation address | Palle Juul Jensens Blv 100, Aarhus, Denmark, 8200                                  |
| Public contact               | Paediatric Department, Aarhus University Hospital, +45 78451471, anjor@clin.au.dk  |
| Scientific contact           | Paediatric Department, Aarhus University Hospital, +45 78451471, anjor@clin.au.dk  |
| Sponsor organisation name    | Aarhus University Hospital   |
| Sponsor organisation address | Palle Juul Jensens blv 100, Aarhus N, Denmark, 8200                                |
| Public contact               | Pediatric Department, Aarhus University Hospital, 0045 78450000, anjor@clin.au.dk  |
| Scientific contact           | Pediatric Department , Aarhus University Hospital, 0045 78451471, anjor@clin.au.dk |

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                       | 25 September 2017 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 06 February 2017  |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 01 March 2017     |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

to evaluate if high dose antioxidant treatment ( per oral) of cystic fibrosis patients can inhibit the oxidative stress mediated inflammation in their lungs-Measured by concentration of desmosine/isodesmosine in the urine

Protection of trial subjects:

To minimize pain in relation to blood sampling the patients were offered local anesthetics or inhalation with 50% N2O +50% O2. No other measures were taken

Background therapy:

Pancreatic enzymes -vitamin supplementation- PEP mask therapy- pulmozyme inhalation

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 01 April 2016 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Denmark: 40 |
| Worldwide total number of subjects   | 40          |
| EEA total number of subjects         | 40          |

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)                     | 26 |

|                           |    |
|---------------------------|----|
| Adolescents (12-17 years) | 14 |
| Adults (18-64 years)      | 0  |
| From 65 to 84 years       | 0  |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Patients were contacted during routine control visits in the outpatient Clinic and asked if they wanted to participate. Recruitment period June 2016-October 2016

### Pre-assignment

Screening details:

41 patients were screened. One produced pseudomonas aeruginosa positive sputum culture during the investigation period and had to be excluded.

### Period 1

|                              |                             |
|------------------------------|-----------------------------|
| Period 1 title               | baseline                    |
| Is this the baseline period? | Yes                         |
| Allocation method            | Non-randomised - controlled |
| Blinding used                | Not blinded                 |

### Arms

|                              |          |
|------------------------------|----------|
| Are arms mutually exclusive? | Yes      |
| <b>Arm title</b>             | Baseline |

Arm description:

7 days without any antiinflammatory treatment

|   |                 |
|---|-----------------|
| Arm type  | No intervention |
| No investigational medicinal product assigned in this arm |                 |

|                  |                      |
|------------------|----------------------|
| <b>Arm title</b> | medical intervention |
|------------------|----------------------|

Arm description:

Pts. received 7 days N-acetyl cysteine 100 mg/kg/ in 3 doses + after that 7 days N-acetylcysteine 200mg/kg/in 3 doses.

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | N-acetylcysteine |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Tablet           |
| Routes of administration               | Oral use         |

Dosage and administration details:

7 days with 100mg/kg/ 24 hrs in 3 divided doses followed by 7 days with 200 mg /kg/24 hrs in 3 divided doses

| Number of subjects in period 1 | Baseline | medical intervention |
|--------------------------------|----------|----------------------|
| Started                        | 20       | 20                   |
| Completed                      | 20       | 20                   |

|   |                             |
|---|-----------------------------|
| <b>Period 2</b>   |                             |
| Period 2 title  | medical intervention        |
| Is this the baseline period?                              | No                          |
| Allocation method   | Non-randomised - controlled |
| Blinding used   | Not blinded                 |
| <b>Arms</b>   |                             |
| <b>Arm title</b>  | baseline                    |
| Arm description:  |                             |
| 7 days with no antiinflammatory treatment                 |                             |
| Arm type  | No intervention             |
| No investigational medicinal product assigned in this arm |                             |

|                                       |          |
|---------------------------------------|----------|
| <b>Number of subjects in period 2</b> | baseline |
| Started                               | 40       |
| Completed                             | 40       |

## Baseline characteristics

### Reporting groups

|  |                      |
|--|----------------------|
| Reporting group title  | Baseline             |
| Reporting group description:<br>7 days without any antiinflammatory treatment  |                      |
| Reporting group title  | medical intervention |
| Reporting group description:<br>Pts. recieved 7 days N-acetyl cysteine 100 mg/kg/ in 3 doses + after that 7 days N-acetylcysteine 200mg/kg/in 3 doses. |                      |

| Reporting group values                                | Baseline | medical intervention | Total |
|---|----------|----------------------|-------|
| Number of subjects                                    | 20       | 20                   | 40    |
| Age categorical                                       |          |                      |       |
| children 2-11: 13<br>adolescents 12-17: 7             |          |                      |       |
| Units: Subjects                                       |          |                      |       |
| In utero  | 0        | 0                    | 0     |
| Preterm newborn infants<br>(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)                                 | 13       | 13                   | 26    |
| Adolescents (12-17 years)                             | 7        | 7                    | 14    |
| Adults (18-64 years)                                  | 0        | 0                    | 0     |
| From 65-84 years                                      | 0        | 0                    | 0     |
| 85 years and over                                     | 0        | 0                    | 0     |
| children  | 0        | 0                    | 0     |
| adolescents   | 0        | 0                    | 0     |
| Gender categorical                                    |          |                      |       |
| female:9<br>Male: 11                                  |          |                      |       |
| Units: Subjects                                       |          |                      |       |
| Female  | 9        | 9                    | 18    |
| Male  | 11       | 11                   | 22    |

### Subject analysis sets

|   |                |
|---|----------------|
| Subject analysis set title  | Pre treatment  |
| Subject analysis set type   | Per protocol   |
| Subject analysis set description:<br>A spot urine was taken at day 7 and 21 - and analyses for desmosine/isodesmosine was carried out and related to urine creatinin values |                |
| Subject analysis set title  | Post treatment |
| Subject analysis set type   | Per protocol   |
| Subject analysis set description:<br>A spot urine was taken at day 7 and 21 - and analyses for desmosine/isodesmosine was carried out and related to urine creatinin values |                |

| Reporting group values                                | Pre treatment | Post treatment |  |
|---|---------------|----------------|--|
| Number of subjects                                    | 20            | 20             |  |
| Age categorical                                       |               |                |  |
| children 2-11: 13<br>adolescents 12-17: 7             |               |                |  |
| 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)                                 | 13            | 13             |  |
| Adolescents (12-17 years)                             | 7             | 7              |  |
| Adults (18-64 years)                                  | 0             | 0              |  |
| From 65-84 years                                      | 0             | 0              |  |
| 85 years and over                                     | 0             | 0              |  |
| children  | 0             | 0              |  |
| adolescents   | 0             | 0              |  |
| Gender categorical                                    |               |                |  |
| female:9<br>Male: 11                                  |               |                |  |
| Units: Subjects                                       |               |                |  |
| Female  | 9             | 9              |  |
| Male  | 11            | 11             |  |

## End points

### End points reporting groups

|   |                      |
|---|----------------------|
| Reporting group title   | Baseline             |
| Reporting group description:<br>7 days without any antiinflammatory treatment   |                      |
| Reporting group title   | medical intervention |
| Reporting group description:<br>Pts. recieved 7 days N-acetyl cysteine 100 mg/kg/ in 3 doses + after that 7 days N-acetylcysteine 200mg/kg/in 3 doses.                      |                      |
| Reporting group title   | baseline             |
| Reporting group description:<br>7 days with no antiinflammatory treatment   |                      |
| Subject analysis set title  | Pre treatment        |
| Subject analysis set type   | Per protocol         |
| Subject analysis set description:<br>A spot urine was taken at day 7 and 21 - and analyses for desmosine/isodesmosine was carried out and related to urine creatinin values |                      |
| Subject analysis set title  | Post treatment       |
| Subject analysis set type   | Per protocol         |
| Subject analysis set description:<br>A spot urine was taken at day 7 and 21 - and analyses for desmosine/isodesmosine was carried out and related to urine creatinin values |                      |

### Primary: change in urine desmosine/isodesmosine excretion

|   |  |
|---|--|
| End point title   | change in urine desmosine/isodesmosine excretion |
| End point description:<br>Spot Urine samples were analysed for desmosine/isodesmosine in ng /ml and related to urine creatinine in mg/ml - making values in ng/mg |  |
| End point type  | Primary  |
| End point timeframe:<br>Measurements were made day 7 and 14   |  |

| End point values              | Baseline             | medical intervention | Pre treatment        | Post treatment       |
|-------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type            | Reporting group      | Reporting group      | Subject analysis set | Subject analysis set |
| Number of subjects analysed   | 20                   | 20                   | 20                   | 20                   |
| Units: ng/mg                  |                      |                      |                      |                      |
| median (full range (min-max)) | 52.4 (32.9 to 100.6) | 50.15 (16.3 to 82.7) | 52.4 (32.9 to 100.6) | 50.15 (16.3 to 82.7) |

### Statistical analyses

|   |                           |
|---|---------------------------|
| Statistical analysis title  | Wilcoxon signed rank test |
| Statistical analysis description:<br>Median and range for values from day 7- and day 14 were calculated and a Wilcoxon signed rank test was calculated between day 7 values and day 14 values |                           |



|   |                                  |
|---|----------------------------------|
| Comparison groups                       | Pre treatment v Post treatment   |
| Number of subjects included in analysis | 40                               |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | other <sup>[1]</sup>             |
| P-value                                 | < 0.05 <sup>[2]</sup>            |
| Method                                  | Wilcoxon (Mann-Whitney)          |
| Parameter estimate                      | Median difference (final values) |
| Point estimate                          | 0.05                             |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | 0.05                             |
| upper limit                             | 0.95                             |
| Variability estimate                    | Standard error of the mean       |

Notes:

[1] - values from 20 patients at day 7 are compared to 20 treated patients values at day 14

[2] - No significant differences were found

## Adverse events

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### Adverse events information<sup>[1]</sup>

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Timeframe for reporting adverse events:

28 days

Adverse event reporting additional description:

clinical examination and anamnestic review at all 4 clinical visits, blood tests

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 19 |
|--------------------|----|

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Frequency threshold for reporting non-serious adverse events: 1 %

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Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: No non-serious adverse effects were observed

## 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.

|      |
|------|
| None |
|------|

Notes: