



## Clinical trial results:

### Anti-inflammatory pulmonal therapy of CF-patients with Amitriptyline and Placebo - Randomised, double-blind, placebo-controlled cohort trial Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2014-003581-25 |
| Trial protocol           | DE             |
| Global end of trial date | 14 June 2019   |

#### Results information

|                                   |  |
|-----------------------------------|--|
| Result version number             | v1 (current)   |
| This version publication date     | 11 November 2021   |
| First version publication date    | 11 November 2021   |
| Summary attachment (see zip file) | Adverse Events information_APAIII (Adverse Events information_APAIII.pdf)<br>Primary endpoint statistical analysis (Primary endpoint statistical analysis.pdf) |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | APA-III |
|-----------------------|---------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | University Hospital Tübingen   |
| Sponsor organisation address | Geissweg 3, Tübingen, Germany, 72076   |
| Public contact               | Dr.med. Andreas Hector, University Children's Hospital, CPCS, +49 70712981341, andreas.hector@med.uni-tuebingen.de |
| Scientific contact           | Dr.med. Andreas Hector, University Children's Hospital, CPCS, +49 70712981341, andreas.hector@med.uni-tuebingen.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                       | 12 June 2019 |
| Is this the analysis of the primary completion data? | Yes          |
| Primary completion date                              | 29 May 2019  |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 14 June 2019 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

Difference in absolute FEV1 % predicted between verum and placebo at week 8 compared to baseline

Protection of trial subjects:

Patient's safety and well-being was taken in consideration during the whole procedure of the trial

Background therapy: -

Evidence for comparator: -

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 20 August 2015 |
| 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 | Germany: 79 |
| Worldwide total number of subjects   | 79          |
| EEA total number of subjects         | 79          |

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)                 | 10 |
| Adults (18-64 years)                      | 66 |
| From 65 to 84 years                       | 3  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

According to study protocol recruitment was planned to start in March 2015 and to be done within 18 months.

Number of cases, statistical considerations, a total of 102 patients had to be included in this study (refer to study protocol chapter 9.1). The last follow-up included into this report took place on June 8th, 2018.

### Pre-assignment

Screening details:

As already mentioned hardly any data are documented concerning the pre-screening process and therefore the reasons, why patients could not be screened for the study.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall trial (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Double blind                   |
| Roles blinded                | Subject, Investigator          |

Blinding implementation details:

The study was done double blinded (patients and treating physicians) but due to the known side effects of amitriptyline it must be feared that physicians as well as patients knew which treatment they got.

### Arms

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

Arm description:

Amitriptyline

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Amitriptyline |
| Investigational medicinal product code | 549-18-8      |
| Other name                             | Elavil        |
| Pharmaceutical forms                   | Capsule       |
| Routes of administration               | Oral use      |

Dosage and administration details:

Amitriptyline 2 x 12.5 mg oral (day 1-14), followed by 2x25mg twice daily (day 15-98).

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | Placebo arm |
|------------------|-------------|

Arm description: -

|  |                       |
|--|-----------------------|
| Arm type                               | Placebo               |
| Investigational medicinal product name | Placebo (corn starch) |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Capsule               |
| Routes of administration               | Oral use              |

Dosage and administration details:

Placebo (corn starch) 2 x 12.5 mg oral (day 1-14), followed by 2x25mg twice daily (day 15-98)

| <b>Number of subjects in period 1</b> | Amitriptyline arm | Placebo arm |
|---------------------------------------|-------------------|-------------|
| Started                               | 42                | 37          |
| Completed                             | 36                | 34          |
| Not completed                         | 6                 | 3           |
| Lost to follow-up                     | 2                 | 1           |
| Protocol deviation                    | 4                 | 2           |

## Baseline characteristics

### Reporting groups

|                                |               |
|--------------------------------|---------------|
| Reporting group title          | Overall trial |
| Reporting group description: - |               |

| Reporting group values   | Overall trial | Total |  |
|--|---------------|-------|--|
| Number of subjects   | 79            | 79    |  |
| Age categorical  |               |       |  |
| The median age was 24 years. The minimum age was 13 years and the maximum was 68 |               |       |  |
| 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)  | 19            | 19    |  |
| Adults (18-64 years)   | 59            | 59    |  |
| From 65-84 years   | 1             | 1     |  |
| 85 years and over  | 0             | 0     |  |
| Gender categorical   |               |       |  |
| Units: Subjects  |               |       |  |
| Female   | 34            | 34    |  |
| Male   | 45            | 45    |  |

## End points

### End points reporting groups

|                                |                   |
|--------------------------------|-------------------|
| Reporting group title          | Amitriptyline arm |
| Reporting group description:   |                   |
| Amitriptyline                  |                   |
| Reporting group title          | Placebo arm       |
| Reporting group description: - |                   |

### Primary: Difference between baseline and week 8 in FEV1%

|  |  |
|--|--|
| End point title  | Difference between baseline and week 8 in FEV1% <sup>[1]</sup> |
| End point description:   |  |
| Difference in absolute FEV1 % predicted between verum and placebo at week 8 compared to baseline |  |
| End point type   | Primary  |
| End point timeframe:   |  |
| 8 weeks  |  |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analyses can be found in the attached chart

| End point values                     | Amitriptyline arm | Placebo arm     |  |  |
|--------------------------------------|-------------------|-----------------|--|--|
| Subject group type                   | Reporting group   | Reporting group |  |  |
| Number of subjects analysed          | 42                | 37              |  |  |
| Units: 40                            |                   |                 |  |  |
| arithmetic mean (standard deviation) | -2.23 (± 9.64)    | -1.34 (± 6.85)  |  |  |

|                                   |  |
|-----------------------------------|--|
| <b>Attachments (see zip file)</b> | Primary endpoint statistical analysis/Primary endpoint statistical |
|-----------------------------------|--|

### Statistical analyses

No statistical analyses for this end point

### Secondary: Absolute and relative FEV1 as 2. Absolute and relative FEV1 as % predicted after 4, 8 and 16 weeks compared to baseline, if not primary

|   |   |
|---|---|
| End point title   | Absolute and relative FEV1 as 2. Absolute and relative FEV1 as % predicted after 4, 8 and 16 weeks compared to baseline, if not primary |
| End point description:  |   |
| Absolute and relative FEV1 as 2. Absolute and relative FEV1 as % predicted after 4, 8 and 16 weeks compared to baseline, if not primary |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| between week 8 and week 16  |   |

| End point values                     | Amitriptyline arm    | Placebo arm          |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed          | 42                   | 37                   |  |  |
| Units: 40                            |                      |                      |  |  |
| arithmetic mean (standard deviation) | 66.71 ( $\pm$ 19.31) | 64.67 ( $\pm$ 21.65) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: FEV1 [L]

|   |           |
|---|-----------|
| End point title   | FEV1 [L]  |
| End point description:<br>Absolute and relative FEV1 increase |           |
| End point type  | Secondary |
| End point timeframe:<br>Until study termination (20 weeks)    |           |

| End point values                     | Amitriptyline arm  | Placebo arm        |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 42                 | 37                 |  |  |
| Units: 40                            |                    |                    |  |  |
| arithmetic mean (standard deviation) | 2.37 ( $\pm$ 0.79) | 2.42 ( $\pm$ 0.93) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Other lung function parameters (FVC) (%)

|                                  |  |
|----------------------------------|--|
| End point title                  | Other lung function parameters (FVC) (%) |
| End point description:           |  |
| End point type                   | Secondary                                |
| End point timeframe:<br>16 weeks |  |

| End point values                     | Amitriptyline arm    | Placebo arm          |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed          | 42                   | 37                   |  |  |
| Units: 40                            |                      |                      |  |  |
| arithmetic mean (standard deviation) | 82.52 ( $\pm$ 18.23) | 85.05 ( $\pm$ 18.10) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Other lung function parameters (FVC) (L)

|                        |  |
|------------------------|--|
| End point title        | Other lung function parameters (FVC) (L) |
| End point description: |  |
| End point type         | Secondary                                |
| End point timeframe:   |  |
| 16 weeks               |  |

| End point values                     | Amitriptyline arm  | Placebo arm        |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 42                 | 37                 |  |  |
| Units: 40                            |                    |                    |  |  |
| arithmetic mean (standard deviation) | 3.39 ( $\pm$ 1.05) | 3.73 ( $\pm$ 0.95) |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

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

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Timeframe for reporting adverse events:

The trial duration and the follow up period

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

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### Dictionary used

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

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|                    |   |
|--------------------|---|
| Dictionary version | 1 |
|--------------------|---|

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Frequency threshold for reporting non-serious adverse events: 0 %

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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: Information regarding Adverse Events can be found in the attached documents

## **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