



## Clinical trial results:

**An 8 week open-label interventional multicenter study to evaluate the lung clearance index as endpoint for clinical trials in cystic fibrosis patients 6 years of age, chronically infected with *Pseudomonas aeruginosa***

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2014-001204-21 |
| Trial protocol           | DE             |
| Global end of trial date | 10 April 2017  |

### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 25 October 2017 |
| First version publication date | 25 October 2017 |

### Trial information

#### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CTBM100CDE02 |
|-----------------------|--------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02248922 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Novartis Pharma AG  |
| Sponsor organisation address | CH-4002, Basel, Switzerland,                                  |
| Public contact               | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |

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? | Yes |

Notes:

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**Results analysis stage**

|  |               |
|--|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 10 April 2017 |
| Is this the analysis of the primary completion data? | No            |

|                                  |               |
|----------------------------------|---------------|
| Global end of trial reached?     | Yes           |
| Global end of trial date         | 10 April 2017 |
| Was the trial ended prematurely? | Yes           |

Notes:

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**General information about the trial**

Main objective of the trial:

The primary objective of the study was to assess the change of LCI after 4 weeks following onset of study drug inhalation versus Baseline.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 27 January 2015 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

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**Population of trial subjects****Subjects enrolled per country**

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Germany: 17 |
| Worldwide total number of subjects   | 17          |
| EEA total number of subjects         | 17          |

Notes:

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**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)                     | 1  |
| Adolescents (12-17 years)                 | 2  |
| Adults (18-64 years)                      | 14 |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

At least 35 patients were planned to be recruited in the study. However, in total, 17 patients entered into the study and completed.

Reason for termination was challenge with enrollment and recruitment. A significant decrease in the eligible patient population was main driver.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| 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>             | Tobramycin inhalation solution(TIS) |

Arm description:

300mg nebulized Tobramycin (Tobramycin inhalation solution(TIS)) twice a day (BID) 28days on / 28 days off

|  |                     |
|--|---------------------|
| Arm type                               | Experimental        |
| Investigational medicinal product name | Tobramycin          |
| Investigational medicinal product code | TBM100              |
| Other name                             |                     |
| Pharmaceutical forms                   | Inhalation solution |
| Routes of administration               | Inhalation use      |

Dosage and administration details:

Tobramycin inhalation solution(TIS) 300mg nebulized inhalation twice a day 28 days on and 28 days off

|                  |                                    |
|------------------|------------------------------------|
| <b>Arm title</b> | Tobramycin inhalation powder (TIP) |
|------------------|------------------------------------|

Arm description:

TOBI Podhaler (Tobramycin inhalation powder(TIP), equivalent dry powder)twice a day (BID) 28days on / 28 days off

|  |                                 |
|--|---------------------------------|
| Arm type                               | Experimental                    |
| Investigational medicinal product name | Tobramycin                      |
| Investigational medicinal product code | TBM100                          |
| Other name                             |                                 |
| Pharmaceutical forms                   | Inhalation powder, hard capsule |
| Routes of administration               | Inhalation use                  |

Dosage and administration details:

Tobramycin inhalation powder (TIP) 112 mg inhalation twice a day 28 days on and 28 days off

| <b>Number of subjects in period 1</b> | Tobramycin<br>inhalation<br>solution(TIS) | Tobramycin<br>inhalation powder<br>(TIP) |
|---------------------------------------|---|--|
| Started                               | 5   | 12                                       |
| Completed                             | 5   | 12                                       |

## Baseline characteristics

### Reporting groups

|   |                                     |
|---|-------------------------------------|
| Reporting group title   | Tobramycin inhalation solution(TIS) |
| Reporting group description:<br>300mg nebulized Tobramycin (Tobramycin inhalation solution(TIS)) twice a day (BID) 28days on / 28 days off        |                                     |
| Reporting group title   | Tobramycin inhalation powder (TIP)  |
| Reporting group description:<br>TOBI Podhaler (Tobramycin inhalation powder(TIP), equivalent dry powder)twice a day (BID) 28days on / 28 days off |                                     |

| Reporting group values                             | Tobramycin inhalation solution(TIS) | Tobramycin inhalation powder (TIP) | Total |
|--|-------------------------------------|------------------------------------|-------|
| Number of subjects                                 | 5                                   | 12                                 | 17    |
| Age categorical<br>Units: Subjects                 |                                     |                                    |       |
| In utero   | 0                                   | 0                                  | 0     |
| Preterm newborn infants (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)                              | 1                                   | 0                                  | 1     |
| Adolescents (12-17 years)                          | 1                                   | 1                                  | 2     |
| Adults (18-64 years)                               | 3                                   | 11                                 | 14    |
| From 65-84 years                                   | 0                                   | 0                                  | 0     |
| 85 years and over                                  | 0                                   | 0                                  | 0     |
| Age Continuous<br>Units: years                     |                                     |                                    |       |
| arithmetic mean                                    | 20.2                                | 28.9                               |       |
| standard deviation                                 | ± 8.26                              | ± 9.79                             | -     |
| Gender, Male/Female<br>Units: Subjects             |                                     |                                    |       |
| Female   | 3                                   | 3                                  | 6     |
| Male   | 2                                   | 9                                  | 11    |
| Race (NIH/OMB)<br>Units: Subjects                  |                                     |                                    |       |
| American Indian or Alaska Native                   | 0                                   | 0                                  | 0     |
| Asian  | 0                                   | 0                                  | 0     |
| Native Hawaiian or Other Pacific Islander          | 0                                   | 0                                  | 0     |
| Black or African American                          | 0                                   | 0                                  | 0     |
| White  | 5                                   | 12                                 | 17    |
| More than one race                                 | 0                                   | 0                                  | 0     |
| Unknown or Not Reported                            | 0                                   | 0                                  | 0     |

## Subject analysis sets

|                            |                 |
|----------------------------|-----------------|
| Subject analysis set title | Tobramycin ALL  |
| Subject analysis set type  | Safety analysis |

Subject analysis set description:

300mg nebulized Tobramycin (Tobramycin inhalation solution(TIS)) or TOBI Podhaler (Tobramycin inhalation powder(TIP), equivalent dry powder)twice a day (BID) 28days on / 28 days off

| Reporting group values                                | Tobramycin ALL |  |  |
|---|----------------|--|--|
| Number of subjects                                    | 17             |  |  |
| Age categorical                                       |                |  |  |
| Units: Subjects                                       |                |  |  |
| In utero  | 0              |  |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0              |  |  |
| Newborns (0-27 days)                                  | 0              |  |  |
| Infants and toddlers (28 days-23<br>months)           | 0              |  |  |
| Children (2-11 years)                                 | 1              |  |  |
| Adolescents (12-17 years)                             | 2              |  |  |
| Adults (18-64 years)                                  | 14             |  |  |
| From 65-84 years                                      | 0              |  |  |
| 85 years and over                                     | 0              |  |  |
| Age Continuous  |                |  |  |
| Units: years  |                |  |  |
| arithmetic mean                                       | 26.4           |  |  |
| standard deviation                                    | ± 9.99         |  |  |
| Gender, Male/Female                                   |                |  |  |
| Units: Subjects                                       |                |  |  |
| Female  | 6              |  |  |
| Male  | 11             |  |  |
| Race (NIH/OMB)  |                |  |  |
| Units: Subjects                                       |                |  |  |
| American Indian or Alaska Native                      | 0              |  |  |
| Asian   | 0              |  |  |
| Native Hawaiian or Other Pacific<br>Islander          | 0              |  |  |
| Black or African American                             | 0              |  |  |
| White   | 17             |  |  |
| More than one race                                    | 0              |  |  |
| Unknown or Not Reported                               | 0              |  |  |

## End points

### End points reporting groups

|  |                                     |
|--|-------------------------------------|
| Reporting group title  | Tobramycin inhalation solution(TIS) |
| Reporting group description:<br>300mg nebulized Tobramycin (Tobramycin inhalation solution(TIS)) twice a day (BID) 28days on / 28 days off   |                                     |
| Reporting group title  | Tobramycin inhalation powder (TIP)  |
| Reporting group description:<br>TOBI Podhaler (Tobramycin inhalation powder(TIP), equivalent dry powder)twice a day (BID) 28days on / 28 days off  |                                     |
| Subject analysis set title   | Tobramycin ALL                      |
| Subject analysis set type  | Safety analysis                     |
| Subject analysis set description:<br>300mg nebulized Tobramycin (Tobramycin inhalation solution(TIS)) or TOBI Podhaler (Tobramycin inhalation powder(TIP), equivalent dry powder)twice a day (BID) 28days on / 28 days off |                                     |

### Primary: Change from Baseline in Lung Clearance Index (LCI) after 4 weeks following onset of study

|  |  |
|--|--|
| End point title  | Change from Baseline in Lung Clearance Index (LCI) after 4 weeks following onset of study <sup>[1]</sup> |
| End point description:<br>The Lung Clearance Index (LCI), measured by Multiple Breath Washout of a tracer gas reflects the obstruction of airways in the lung. A LCI of 7.5 and below is normal. No statistical analysis as there was no comparison and only one reporting group. No statistical analysis as there was no comparison and only one reporting group. |  |
| End point type   | Primary  |
| End point timeframe:<br>Baseline, week 4   |  |

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: No statistical analysis as there was no comparison and only one reporting group.

| End point values                    | Tobramycin ALL       |  |  |  |
|-------------------------------------|----------------------|--|--|--|
| Subject group type                  | Subject analysis set |  |  |  |
| Number of subjects analysed         | 17                   |  |  |  |
| Units: score                        |                      |  |  |  |
| least squares mean (standard error) |                      |  |  |  |
| Baseline                            | 17.985 (± 1.1494)    |  |  |  |
| Week 4                              | 17.101 (± 0.8409)    |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline of forced expiratory volume at 1 second (FEV1) after 4 weeks following onset of study

|                 |  |
|-----------------|--|
| End point title | Change from Baseline of forced expiratory volume at 1 second |
|-----------------|--|

(FEV1) after 4 weeks following onset of study

End point description:

Change of FEV1 (Forced expiry volume in the first second) measured by Spirometry

End point type Secondary

End point timeframe:

Baseline, week 4

|                                     |                           |  |  |  |
|-------------------------------------|---------------------------|--|--|--|
| <b>End point values</b>             | Tobramycin<br>ALL         |  |  |  |
| Subject group type                  | Subject analysis set      |  |  |  |
| Number of subjects analysed         | 17                        |  |  |  |
| Units: % Predicted                  |                           |  |  |  |
| least squares mean (standard error) |                           |  |  |  |
| Baseline                            | 76.964 ( $\pm$<br>4.5121) |  |  |  |
| Week 4                              | 77.481 ( $\pm$<br>4.9877) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline of colony-forming units (CFU) after 4 weeks following onset of study

End point title Change from Baseline of colony-forming units (CFU) after 4 weeks following onset of study

End point description:

Microbacterial density of Pseudomonas aeruginosa in Sputum-Samples in CFU (Colony Forming Units) per gram sputum.

End point type Secondary

End point timeframe:

Baseline, week 4

|                                     |                              |  |  |  |
|-------------------------------------|------------------------------|--|--|--|
| <b>End point values</b>             | Tobramycin<br>ALL            |  |  |  |
| Subject group type                  | Subject analysis set         |  |  |  |
| Number of subjects analysed         | 17                           |  |  |  |
| Units: 1/mL                         |                              |  |  |  |
| least squares mean (standard error) |                              |  |  |  |
| Baseline n=15                       | 56594.3 ( $\pm$<br>28018.89) |  |  |  |
| Week 4 n=10                         | 26113.0 ( $\pm$<br>27280.98) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Lung Clearance Index (LCI) after 1 week

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in Lung Clearance Index (LCI) after 1 week |
|-----------------|---|

End point description:

The Lung Clearance Index (LCI), measured by Multiple Breath Washout of a tracer gas reflects the obstruction of airways in the lung. A LCI of 7.5 and below is normal,

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

End point timeframe:

Baseline, week 1

| End point values                    | Tobramycin<br>ALL         |  |  |  |
|-------------------------------------|---------------------------|--|--|--|
| Subject group type                  | Subject analysis set      |  |  |  |
| Number of subjects analysed         | 17                        |  |  |  |
| Units: score                        |                           |  |  |  |
| least squares mean (standard error) |                           |  |  |  |
| Baseline                            | 17.985 ( $\pm$<br>1.1494) |  |  |  |
| Week 1                              | 17.506 ( $\pm$<br>1.0002) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change of Lung Clearance Index (LCI) between week 4 (end of study drug inhalation in the current treatment cycle) and week 8 (prior to start of study drug inhalation in the following treatment cycle)

|                 |   |
|-----------------|---|
| End point title | Change of Lung Clearance Index (LCI) between week 4 (end of study drug inhalation in the current treatment cycle) and week 8 (prior to start of study drug inhalation in the following treatment cycle) |
|-----------------|---|

End point description:

The Lung Clearance Index (LCI), measured by Multiple Breath Washout of a tracer gas reflects the obstruction of airways in the lung. A LCI of 7.5 and below is normal,

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

End point timeframe:

week 4, week 8

|                                     |                           |  |  |  |
|-------------------------------------|---------------------------|--|--|--|
| <b>End point values</b>             | Tobramycin<br>ALL         |  |  |  |
| Subject group type                  | Subject analysis set      |  |  |  |
| Number of subjects analysed         | 17                        |  |  |  |
| Units: score                        |                           |  |  |  |
| least squares mean (standard error) |                           |  |  |  |
| Week 4                              | 17.101 ( $\pm$<br>0.8409) |  |  |  |
| Week 8                              | 16.489 ( $\pm$<br>1.1473) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change of forced expiratory volume at 1 second(FEV1) between week 4 (end of study drug inhalation in the current treatment cycle) and week 8 (prior to start of study drug inhalation in the following treatment cycle)

|                        |   |
|------------------------|---|
| End point title        | Change of forced expiratory volume at 1 second(FEV1) between week 4 (end of study drug inhalation in the current treatment cycle) and week 8 (prior to start of study drug inhalation in the following treatment cycle) |
| End point description: | Change of FEV1 (Forced expiry volume in the first second) measured by Spirometry  |
| End point type         | Secondary   |
| End point timeframe:   | week 4, week 8  |

|                                     |                           |  |  |  |
|-------------------------------------|---------------------------|--|--|--|
| <b>End point values</b>             | Tobramycin<br>ALL         |  |  |  |
| Subject group type                  | Subject analysis set      |  |  |  |
| Number of subjects analysed         | 17                        |  |  |  |
| Units: % Predicted                  |                           |  |  |  |
| least squares mean (standard error) |                           |  |  |  |
| Week 4                              | 77.481 ( $\pm$<br>4.9877) |  |  |  |
| Week 8                              | 78.705 ( $\pm$<br>5.4782) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change of colony-forming units (CFU) between week 4 (end of study drug inhalation in the current treatment cycle) and week 8 (prior to start of study drug inhalation in the following treatment cycle)

|                 |  |
|-----------------|--|
| End point title | Change of colony-forming units (CFU) between week 4 (end of study drug inhalation in the current treatment cycle) and week |
|-----------------|--|

|  |
|--|
| 8 (prior to start of study drug inhalation in the following treatment cycle) |
|--|

End point description:

Microbacterial density of *Pseudomonas aeruginosa* in Sputum-Samples in CFU (Colony Forming Units) per gram sputum.

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

End point timeframe:

week 4, week 8

| End point values                    | Tobramycin<br>ALL       |  |  |  |
|-------------------------------------|-------------------------|--|--|--|
| Subject group type                  | Subject analysis set    |  |  |  |
| Number of subjects analysed         | 17                      |  |  |  |
| Units: 1/mL                         |                         |  |  |  |
| least squares mean (standard error) |                         |  |  |  |
| Week 4 n=10                         | 26113.0 (±<br>27280.98) |  |  |  |
| Week 8 n=15                         | 56285.0 (±<br>28022.28) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 19.0   |

### Reporting groups

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Tobramycin@Inhalation@Solution |
|-----------------------|--------------------------------|

Reporting group description:

Tobramycin@Inhalation@Solution

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | Tobramycin@Inhalation@Powder |
|-----------------------|------------------------------|

Reporting group description:

Tobramycin@Inhalation@Powder

| Serious adverse events                            | Tobramycin@Inhalation@Solution | Tobramycin@Inhalation@Powder |  |
|---|--------------------------------|------------------------------|--|
| Total subjects affected by serious adverse events |                                |                              |  |
| subjects affected / exposed                       | 0 / 5 (0.00%)                  | 0 / 12 (0.00%)               |  |
| number of deaths (all causes)                     | 0                              | 0                            |  |
| number of deaths resulting from adverse events    | 0                              | 0                            |  |

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

| Non-serious adverse events                            | Tobramycin@Inhalation@Solution | Tobramycin@Inhalation@Powder |  |
|---|--------------------------------|------------------------------|--|
| Total subjects affected by non-serious adverse events |                                |                              |  |
| subjects affected / exposed                           | 2 / 5 (40.00%)                 | 3 / 12 (25.00%)              |  |
| Investigations  |                                |                              |  |
| Forced expiratory volume decreased                    |                                |                              |  |
| subjects affected / exposed                           | 0 / 5 (0.00%)                  | 1 / 12 (8.33%)               |  |
| occurrences (all)                                     | 0                              | 1                            |  |
| Injury, poisoning and procedural complications        |                                |                              |  |
| Sunburn   |                                |                              |  |
| subjects affected / exposed                           | 1 / 5 (20.00%)                 | 0 / 12 (0.00%)               |  |
| occurrences (all)                                     | 1                              | 0                            |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Gastrointestinal disorders                      |                |                |  |
| Abdominal pain upper                            |                |                |  |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 12 (8.33%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| Cough   |                |                |  |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 12 (8.33%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Haemoptysis                                     |                |                |  |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 12 (0.00%) |  |
| occurrences (all)                               | 1              | 0              |  |
| Obstructive airways disorder                    |                |                |  |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 12 (8.33%) |  |
| occurrences (all)                               | 0              | 1              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date           | Amendment   |
|----------------|---|
| 28 May 2015    | <p>Amendment 1: The rationale for changes in protocol amendment 1 were as follows:</p> <ol style="list-style-type: none"><li>1. To clarify the LCI assessment, and to align the protocol with the standard assessment approach for LCI of the device manufacturer. The revised section 7.4.1 reflects now the workflow implemented in the Exhalyzer D device by the actual "Spiroware" software version. Following Investigator-feedback, the upper limit for the FRC coefficient of variation had been increased from 10% to 25% to help reducing the number of MBW measurements needed in pediatric CF patients with moderate lung disease. In addition, this change allowed for the documentation of values for LCI and FRC which had been automatically calculated by the device-software. A more detailed and step-by-step description for the LCI assessment made it easier for the study team to follow the protocol.</li><li>2. To add the change of pulmonary air trapping after 1 week, 4 weeks, and 8 weeks versus baseline to the protocol as an explorative objective. Air trapping was assessed by the difference in FRC measured by bodyplethysmography (FRCples) and FRC measured by MBW (FRCMBW). In this study, spirometry was done by bodyplethysmography. Thus, FRCples was already documented in the source documents. Beneficial effects of treatment with inhaled tobramycin could include a reduction of air trapping by recruitment of lung units previously not contributing to ventilation. If the time constant in newly recruited units was slower, ventilation inhomogeneity, and therefore LCI, could increase despite the positive treatment effect</li><li>3. Following feedback of investigators, the guidance for the spirometric timeframe had been updated to allow for a more flexible assessment planning.</li></ol> |
| 03 August 2015 | <p>Amendment 2: The rationale for changes in protocol amendment 2 was to allow for a more clear and detailed documentation of screening failures with a following re-screening of the patient. In order to limit eCRF page numbers per patient and to optimize the database structure and thus the usability of the data capturing system, a change of the individual number for patients who were re-screened were permitted. Furthermore, the change of patient no. in re-screened patients allowed for a unique and well matched visit numbering in the data capturing and the study management system.</p>  |

Notes:

### 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.

Reason for termination was challenge with enrollment and recruitment. A significant decrease in the eligible patient population was main driver.

Notes: