



## Clinical trial results:

### A Prospective, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of BAY 41-6551 as Adjunctive Therapy in Intubated and Mechanically-Ventilated Patients with Gram-Negative Pneumonia

#### Summary

|                          |                                  |
|--------------------------|----------------------------------|
| EudraCT number           | 2008-000906-35                   |
| Trial protocol           | CZ HU NL BE ES FR LV GR PT IT PL |
| Global end of trial date | 07 April 2017                    |

#### Results information

|                                |  |
|--------------------------------|--|
| Result version number          | v2 (current)   |
| This version publication date  | 20 July 2018   |
| First version publication date | 12 April 2018  |
| Version creation reason        | <ul style="list-style-type: none"><li>• Correction of full data set XML requested by Service desk for issue solving.</li></ul> |

#### Trial information

##### Trial identification

|                       |                  |
|-----------------------|------------------|
| Sponsor protocol code | BAY41-6551/13085 |
|-----------------------|------------------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Bayer AG   |
| Sponsor organisation address | Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368                 |
| Public contact               | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com |
| Scientific contact           | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com |

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                       | 26 January 2018 |
| Is this the analysis of the primary completion data? | No              |

|                                  |               |
|----------------------------------|---------------|
| Global end of trial reached?     | Yes           |
| Global end of trial date         | 07 April 2017 |
| Was the trial ended prematurely? | No            |

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate that as adjunctive therapy to IV antibiotics, BAY 41-6551 400 mg (amikacin as free base) administered as an aerosol by the PDDS Clinical every 12 hours is safe and more effective than placebo (aerosolized normal saline) administered as an aerosol by the PDDS Clinical every 12 hours, in intubated and mechanically-ventilated patients with Gram-negative pneumonia.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 13 April 2013 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | Yes           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                       |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Turkey: 3             |
| Country: Number of subjects enrolled | Belgium: 11           |
| Country: Number of subjects enrolled | Netherlands: 9        |
| Country: Number of subjects enrolled | France: 64            |
| Country: Number of subjects enrolled | Greece: 13            |
| Country: Number of subjects enrolled | Spain: 29             |
| Country: Number of subjects enrolled | Israel: 18            |
| Country: Number of subjects enrolled | Portugal: 1           |
| Country: Number of subjects enrolled | Hungary: 30           |
| Country: Number of subjects enrolled | Poland: 4             |
| Country: Number of subjects enrolled | Russian Federation: 8 |
| Country: Number of subjects enrolled | Ukraine: 7            |
| Country: Number of subjects enrolled | Brazil: 47            |
| Country: Number of subjects enrolled | Colombia: 9           |
| Country: Number of subjects enrolled | Mexico: 25            |
| Country: Number of subjects enrolled | Philippines: 10       |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Korea, Republic of: 19 |
| Country: Number of subjects enrolled | Taiwan: 18             |
| Country: Number of subjects enrolled | Thailand: 6            |
| Country: Number of subjects enrolled | China: 199             |
| Country: Number of subjects enrolled | Japan: 63              |
| Country: Number of subjects enrolled | United States: 90      |
| Country: Number of subjects enrolled | Canada: 17             |
| Country: Number of subjects enrolled | Australia: 9           |
| Country: Number of subjects enrolled | Czech Republic: 3      |
| Worldwide total number of subjects   | 712                    |
| EEA total number of subjects         | 164                    |

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)                      | 326 |
| From 65 to 84 years                       | 335 |
| 85 years and over                         | 51  |

## Subject disposition

### Recruitment

Recruitment details:

To shorten the time required to obtain data from the 2 clinical studies of Amikacin Inhale Phase 3 program, Bayer and the FDA decided that the results of studies NCT01799993 and NCT00805168 should be consolidated into a single report. The studies were conducted at 166 centers across 25 countries, between 22 APR 2013 (FPFV) and 07 APR 2017 (LPLV).

### Pre-assignment

Screening details:

A total of 807 subjects were screened, of which 725 subjects were randomized for the 2 studies, 712 subjects were treated with study treatment per exposure data in EDC; 354 received aerosolized amikacin inhale and 358 received placebo.

### 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          |

### Arms

|                              |                              |
|------------------------------|------------------------------|
| Are arms mutually exclusive? | No                           |
| <b>Arm title</b>             | Amikacin inhale (BAY41-6551) |

Arm description:

Subjects received 400 mg (3.2 mL) aerosolized Amikacin (BAY41-6551) solution every 12 hours via Pulmonary Drug Delivery System (PDDS) Clinical from Day 1 to Day 10.

|  |                     |
|--|---------------------|
| Arm type                               | Experimental        |
| Investigational medicinal product name | Amikacin inhale     |
| Investigational medicinal product code | BAY41-6551          |
| Other name                             |                     |
| Pharmaceutical forms                   | Inhalation solution |
| Routes of administration               | Inhalation use      |

Dosage and administration details:

Subjects received 400 mg (3.2 mL) aerosolized Amikacin (BAY41-6551) solution every 12 hours via PDDS Clinical from Day 1 to Day 10.

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

Arm description:

Subjects received 3.2 mL aerosolized placebo solution every 12 hours via PDDS Clinical from Day 1 to Day 10.

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

Dosage and administration details:

Subjects received 3.2 mL aerosolized placebo solution every 12 hours via PDDS Clinical from Day 1 to Day 10.

| <b>Number of subjects in period 1</b>          | <b>Amikacin inhale<br/>(BAY41-6551)</b> | <b>Placebo</b> |
|--|---|----------------|
| Started  | 362                                     | 363            |
| ITT population                                 | 354                                     | 358            |
| mITT population                                | 255                                     | 253            |
| Completed                                      | 229                                     | 235            |
| Not completed                                  | 133                                     | 128            |
| Deterioration of general conditions            | 2                                       | -              |
| Protocol driven decision point                 | -                                       | 3              |
| Didn't complete CRF page "End of<br>Follow-up" | 30                                      | 40             |
| Adverse event                                  | 1                                       | -              |
| Screen failure                                 | -                                       | 1              |
| Non-compliance with medical device             | 1                                       | -              |
| Withdrawal by parent/guardian/LAR              | 5                                       | 3              |
| Withdrawal by parent/guardian                  | -                                       | 1              |
| Consent withdrawn by subject                   | 23                                      | 24             |
| Recovery                                       | -                                       | 1              |
| Logistical difficulties                        | 1                                       | -              |
| Protocol violation                             | 1                                       | 1              |
| Death  | 61                                      | 45             |
| Unknown  | 1                                       | -              |
| Subject didn't want to return for<br>follow-up | -                                       | 1              |
| Lost to follow-up                              | 5                                       | 8              |
| Protocol deviation                             | 1                                       | -              |
| Lack of efficacy                               | 1                                       | -              |

## Baseline characteristics

### Reporting groups

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

| Reporting group values  | Overall Trial | Total |  |
|---|---------------|-------|--|
| Number of subjects  | 712           | 712   |  |
| Age categorical   |               |       |  |
| Units: Subjects   |               |       |  |
| <18   | 0             | 0     |  |
| 18 to <45   | 91            | 91    |  |
| 18 to <65   | 235           | 235   |  |
| 65 to <75   | 175           | 175   |  |
| >= 75   | 211           | 211   |  |
| Age continuous  |               |       |  |
| Units: years  |               |       |  |
| arithmetic mean   | 63.9          |       |  |
| standard deviation  | ± 16.42       | -     |  |
| Gender categorical  |               |       |  |
| Units: Subjects   |               |       |  |
| Female  | 214           | 214   |  |
| Male  | 498           | 498   |  |
| Ethnicity   |               |       |  |
| Units: Subjects   |               |       |  |
| Not Hispanic or Latino  | 512           | 512   |  |
| Hispanic or Latino  | 104           | 104   |  |
| Not reported  | 96            | 96    |  |
| APACHE II score   |               |       |  |
| Subjects who met all of the inclusion criteria and none of the exclusion criteria were stratified by geographic region (or country) and disease severity using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and randomized in a 1:1 ratio to one of the two treatment groups. |               |       |  |
| Units: Subjects   |               |       |  |
| <20   | 373           | 373   |  |
| >=20  | 339           | 339   |  |
| CPIS  |               |       |  |
| The components of the Clinical Pulmonary Infection Score (CPIS) were collected, and the scores were calculated.   |               |       |  |
| Units: Point  |               |       |  |
| arithmetic mean   | 7.0           |       |  |
| standard deviation  | ± 1.34        | -     |  |

### Subject analysis sets

|  |                    |
|--|--------------------|
| Subject analysis set title   | ITT                |
| Subject analysis set type  | Intention-to-treat |
| Subject analysis set description:  |                    |
| Included all subjects who were treated with at least one dose of study drug. |                    |
| Subject analysis set title   | mITT               |

|  |   |
|--|---|
| Subject analysis set type  | Modified intention-to-treat                 |
| Subject analysis set description:<br>Included all subjects who had a culture-confirmed Gram-negative bacteria that had been treated with at least one dose of study treatment, and had an APACHE II score $\geq 10$ at the time of diagnosis of pneumonia. |   |
| Subject analysis set title   | ITT for Safety population                   |
| Subject analysis set type  | Safety analysis                             |
| Subject analysis set description:<br>Included all subjects in ITT analysis set who were analyzed as treated for safety analyses.   |   |
| Subject analysis set title   | ITT for Safety population - Amikacin inhale |
| Subject analysis set type  | Safety analysis                             |
| Subject analysis set description:<br>Included all subject in ITT analysis set who were analyzed as treated with Amikacin for safety analyses.  |   |
| Subject analysis set title   | ITT for Safety population - Placebo         |
| Subject analysis set type  | Safety analysis                             |
| Subject analysis set description:<br>Included all subject in ITT analysis set who were analyzed as treated with placebo for safety analyses.   |   |
| Subject analysis set title   | ITT - Amikacin inhale                       |
| Subject analysis set type  | Intention-to-treat                          |
| Subject analysis set description:<br>Included all subject in ITT analysis set who were treated with Amikacin   |   |
| Subject analysis set title   | ITT - Placebo                               |
| Subject analysis set type  | Intention-to-treat                          |
| Subject analysis set description:<br>Included all subject in ITT analysis set who were treated with placebo  |   |

| Reporting group values  | ITT   | mITT  | ITT for Safety population |
|---|-------|-------|---------------------------|
| Number of subjects  | 712   | 508   | 712                       |
| Age categorical<br>Units: Subjects  |       |       |                           |
| <18   |       |       |                           |
| 18 to <45   |       |       |                           |
| 18 to <65   |       |       |                           |
| 65 to <75   |       |       |                           |
| $\geq 75$   |       |       |                           |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation   | $\pm$ | $\pm$ | $\pm$                     |
| Gender categorical<br>Units: Subjects   |       |       |                           |
| Female  |       |       |                           |
| Male  |       |       |                           |
| Ethnicity<br>Units: Subjects  |       |       |                           |
| Not Hispanic or Latino  |       |       |                           |
| Hispanic or Latino  |       |       |                           |
| Not reported  |       |       |                           |
| APACHE II score   |       |       |                           |
| Subjects who met all of the inclusion criteria and none of the exclusion criteria were stratified by geographic region (or country) and disease severity using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and randomized in a 1:1 ratio to one of the two treatment groups. |       |       |                           |

|   |   |   |   |
|---|---|---|---|
| Units: Subjects   |   |   |   |
| <20   |   |   |   |
| >=20  |   |   |   |
| CPIS  |   |   |   |
| The components of the Clinical Pulmonary Infection Score (CPIS) were collected, and the scores were calculated. |   |   |   |
| Units: Point  |   |   |   |
| arithmetic mean   |   |   |   |
| standard deviation  | ± | ± | ± |

| Reporting group values  | ITT for Safety population - Amikacin inhale | ITT for Safety population - Placebo | ITT - Amikacin inhale |
|---|---|-------------------------------------|-----------------------|
| Number of subjects  | 353   | 359                                 | 354                   |
| Age categorical   |   |                                     |                       |
| Units: Subjects   |   |                                     |                       |
| <18   |   |                                     | 0                     |
| 18 to <45   |   |                                     | 38                    |
| 18 to <65   |   |                                     | 130                   |
| 65 to <75   |   |                                     | 92                    |
| >= 75   |   |                                     | 94                    |
| Age continuous  |   |                                     |                       |
| Units: years  |   |                                     |                       |
| arithmetic mean   |   |                                     | 63.8                  |
| standard deviation  | ±   | ±                                   | ± 15.78               |
| Gender categorical  |   |                                     |                       |
| Units: Subjects   |   |                                     |                       |
| Female  |   |                                     | 107                   |
| Male  |   |                                     | 247                   |
| Ethnicity   |   |                                     |                       |
| Units: Subjects   |   |                                     |                       |
| Not Hispanic or Latino  |   |                                     | 262                   |
| Hispanic or Latino  |   |                                     | 49                    |
| Not reported  |   |                                     | 43                    |
| APACHE II score   |   |                                     |                       |
| Subjects who met all of the inclusion criteria and none of the exclusion criteria were stratified by geographic region (or country) and disease severity using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and randomized in a 1:1 ratio to one of the two treatment groups. |   |                                     |                       |
| Units: Subjects   |   |                                     |                       |
| <20   |   |                                     | 187                   |
| >=20  |   |                                     | 167                   |
| CPIS  |   |                                     |                       |
| The components of the Clinical Pulmonary Infection Score (CPIS) were collected, and the scores were calculated.   |   |                                     |                       |
| Units: Point  |   |                                     |                       |
| arithmetic mean   |   |                                     | 7.1                   |
| standard deviation  | ±   | ±                                   | ± 1.38                |

| Reporting group values | ITT - Placebo |  |  |
|------------------------|---------------|--|--|
| Number of subjects     | 358           |  |  |
| Age categorical        |               |  |  |
| Units: Subjects        |               |  |  |
| <18                    | 0             |  |  |



|   |         |  |  |
|---|---------|--|--|
| 18 to <45   | 53      |  |  |
| 18 to <65   | 105     |  |  |
| 65 to <75   | 83      |  |  |
| >= 75   | 117     |  |  |
| Age continuous  |         |  |  |
| Units: years  |         |  |  |
| arithmetic mean   | 64.1    |  |  |
| standard deviation  | ± 17.04 |  |  |
| Gender categorical  |         |  |  |
| Units: Subjects   |         |  |  |
| Female  | 107     |  |  |
| Male  | 251     |  |  |
| Ethnicity   |         |  |  |
| Units: Subjects   |         |  |  |
| Not Hispanic or Latino  | 250     |  |  |
| Hispanic or Latino  | 55      |  |  |
| Not reported  | 53      |  |  |
| APACHE II score   |         |  |  |
| Subjects who met all of the inclusion criteria and none of the exclusion criteria were stratified by geographic region (or country) and disease severity using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and randomized in a 1:1 ratio to one of the two treatment groups. |         |  |  |
| Units: Subjects   |         |  |  |
| <20   | 186     |  |  |
| >=20  | 172     |  |  |
| CPIS  |         |  |  |
| The components of the Clinical Pulmonary Infection Score (CPIS) were collected, and the scores were calculated.   |         |  |  |
| Units: Point  |         |  |  |
| arithmetic mean   | 6.9     |  |  |
| standard deviation  | ± 1.29  |  |  |

## End points

### End points reporting groups

|  |   |
|--|---|
| Reporting group title  | Amikacin inhale (BAY41-6551)                |
| Reporting group description:<br>Subjects received 400 mg (3.2 mL) aerosolized Amikacin (BAY41-6551) solution every 12 hours via Pulmonary Drug Delivery System (PDDS) Clinical from Day 1 to Day 10.   |   |
| Reporting group title  | Placebo                                     |
| Reporting group description:<br>Subjects received 3.2 mL aerosolized placebo solution every 12 hours via PDDS Clinical from Day 1 to Day 10.   |   |
| Subject analysis set title   | ITT   |
| Subject analysis set type  | Intention-to-treat                          |
| Subject analysis set description:<br>Included all subjects who were treated with at least one dose of study drug.  |   |
| Subject analysis set title   | mITT  |
| Subject analysis set type  | Modified intention-to-treat                 |
| Subject analysis set description:<br>Included all subjects who had a culture-confirmed Gram-negative bacteria that had been treated with at least one dose of study treatment, and had an APACHE II score $\geq 10$ at the time of diagnosis of pneumonia. |   |
| Subject analysis set title   | ITT for Safety population                   |
| Subject analysis set type  | Safety analysis                             |
| Subject analysis set description:<br>Included all subjects in ITT analysis set who were analyzed as treated for safety analyses.   |   |
| Subject analysis set title   | ITT for Safety population - Amikacin inhale |
| Subject analysis set type  | Safety analysis                             |
| Subject analysis set description:<br>Included all subject in ITT analysis set who were analyzed as treated with Amikacin for safety analyses.  |   |
| Subject analysis set title   | ITT for Safety population - Placebo         |
| Subject analysis set type  | Safety analysis                             |
| Subject analysis set description:<br>Included all subject in ITT analysis set who were analyzed as treated with placebo for safety analyses.   |   |
| Subject analysis set title   | ITT - Amikacin inhale                       |
| Subject analysis set type  | Intention-to-treat                          |
| Subject analysis set description:<br>Included all subject in ITT analysis set who were treated with Amikacin   |   |
| Subject analysis set title   | ITT - Placebo                               |
| Subject analysis set type  | Intention-to-treat                          |
| Subject analysis set description:<br>Included all subject in ITT analysis set who were treated with placebo  |   |
| <b>Primary: Survival through LFU visit</b>   |   |
| End point title  | Survival through LFU visit                  |
| End point description:<br>The primary efficacy variable is Survival through the late follow-up (LFU) visit. Survival is achieved when the subject is alive through the LFU visit. No other factors are considered in the evaluation of survival.           |   |
| End point type   | Primary                                     |
| End point timeframe:<br>Up to 28-32 days after start of study treatment  |   |

| End point values                   | Amikacin inhale (BAY41-6551) | Placebo            |  |  |
|------------------------------------|------------------------------|--------------------|--|--|
| Subject group type                 | Reporting group              | Reporting group    |  |  |
| Number of subjects analysed        | 255 <sup>[1]</sup>           | 253 <sup>[2]</sup> |  |  |
| Units: Subjects                    |                              |                    |  |  |
| Clinical Success (Survive)         | 191                          | 196                |  |  |
| Clinical Failure (Did not survive) | 64                           | 57                 |  |  |

Notes:

[1] - mITT population

[2] - mITT population

## Statistical analyses

| Statistical analysis title | Survival rates through LFU visit |
|----------------------------|----------------------------------|
|----------------------------|----------------------------------|

Statistical analysis description:

The primary analysis compared the Survival rates through LFU visit of patients in the amikacin inhale group versus the patients in the placebo group, using the combined data from studies 13084 and 13085. A Cochran-Mantel-Haenszel (CMH) test of general association, adjusting for randomized stratum (based on APACHE II score as a measure of disease severity) and geographic region was performed as the primary efficacy analysis.

|   |  |
|---|--|
| Comparison groups                       | Placebo v Amikacin inhale (BAY41-6551) |
| Number of subjects included in analysis | 508                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | = 0.4263                               |
| Method                                  | Cochran-Mantel-Haenszel                |
| Parameter estimate                      | Odds ratio (OR)                        |
| Point estimate                          | 0.841                                  |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | 0.554                                  |
| upper limit                             | 1.277                                  |

## Secondary: Adjudicated pneumonia-related mortality through LFU visit

|                 |   |
|-----------------|---|
| End point title | Adjudicated pneumonia-related mortality through LFU visit |
|-----------------|---|

End point description:

Death through LFU visit was adjudicated as pneumonia-related or pneumonia-unrelated for subjects in the amikacin inhale group and subjects in the placebo group.

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

End point timeframe:

Up to 28-32 days after start of study treatment

| End point values              | Amikacin inhale (BAY41-6551) | Placebo           |  |  |
|-------------------------------|------------------------------|-------------------|--|--|
| Subject group type            | Reporting group              | Reporting group   |  |  |
| Number of subjects analysed   | 64 <sup>[3]</sup>            | 57 <sup>[4]</sup> |  |  |
| Units: Subjects               |                              |                   |  |  |
| Pneumonia-related mortality   | 43                           | 36                |  |  |
| Pneumonia-unrelated mortality | 21                           | 21                |  |  |

Notes:

[3] - Participants who died through LFU visit in mITT population set

[4] - Participants who died through LFU visit in mITT population set

## Statistical analyses

| Statistical analysis title | Pneumonia-related mortality through LFU visit |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

Pneumonia-related mortality through LFU visit was formally tested to determine if the difference between the amikacin inhale group versus the placebo group was statistically significant. The null hypothesis of no difference between amikacin inhale and placebo was tested using an unadjusted chi-square test in the mITT population.

|   |  |
|---|--|
| Comparison groups                       | Amikacin inhale (BAY41-6551) v Placebo |
| Number of subjects included in analysis | 121                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | = 0.6421                               |
| Method                                  | Chi-squared                            |

## Secondary: Early Clinical Response

|                 |                         |
|-----------------|-------------------------|
| End point title | Early Clinical Response |
|-----------------|-------------------------|

End point description:

Early Clinical Response was determined by the following: 1. CPIS scoring at Days 3, 5, and 10 compared to baseline (a. On Day 3, CPIS increase from baseline by at least 2 points was considered a failure. b. On Day 5, CPIS decrease from baseline of at least 1 point was not a failure. CPIS of no change from baseline was considered a failure. Any CPIS increase from baseline was a failure. c. On Day 10, CPIS decrease from baseline of at least 2 points was not a failure. CPIS decrease of only 1 point is a failure. CPIS of no change was considered a failure. Any CPIS increase from baseline was a failure.). 2. All-cause mortality through EOT visit was a failure. 3. The development of empyema or lung abscess through the EOT visit was a failure.

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

End point timeframe:

Up to 10 days after start of study treatment.

| End point values                  | Amikacin inhale (BAY41-6551) | Placebo            |  |  |
|-----------------------------------|------------------------------|--------------------|--|--|
| Subject group type                | Reporting group              | Reporting group    |  |  |
| Number of subjects analysed       | 255 <sup>[5]</sup>           | 253 <sup>[6]</sup> |  |  |
| Units: Subjects                   |                              |                    |  |  |
| Early Clinical Response - Success | 149                          | 145                |  |  |
| Early Clinical Response - Failure | 106                          | 108                |  |  |

Notes:

[5] - mITT population

[6] - mITT population

## Statistical analyses

|                                   |                         |
|-----------------------------------|-------------------------|
| <b>Statistical analysis title</b> | Early Clinical Response |
|-----------------------------------|-------------------------|

Statistical analysis description:

Early Clinical Response was formally tested to determine if the difference between the amikacin inhale group versus the placebo group was statistically significant. The null hypothesis of no difference between amikacin inhale and placebo was tested using an unadjusted chi-square test in the mITT population.

|   |  |
|---|--|
| Comparison groups                       | Amikacin inhale (BAY41-6551) v Placebo |
| Number of subjects included in analysis | 508                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | = 0.7984                               |
| Method                                  | Chi-squared                            |

## Secondary: Number of days on mechanical ventilation through the LFU visit

|                 |  |
|-----------------|--|
| End point title | Number of days on mechanical ventilation through the LFU visit |
|-----------------|--|

End point description:

Number of days on mechanical ventilator was summarized by descriptive statistics. Duration was defined as the number of days from the date of first study drug through the LFU visit. For subjects who lived through the LFU visit, the ventilation days were actual days on ventilation with a maximum value of 28 days. For subjects who died after Day 28 but on or before their LFU visit, the days on ventilator was censored at 28 days. For subjects who died or discontinued off ventilation, the number of days on ventilation was actual days on ventilation with a maximum value of 28 days. For subjects who died or discontinued on ventilation, the number of days on ventilation was 28 days. Further analysis of the number of days on mechanical ventilator was to be performed with censoring at Day 28 for subset of subjects on ventilation without censoring.

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

End point timeframe:

Up to 28-32 days after start of study treatment

| <b>End point values</b>              | Amikacin inhale (BAY41-6551) | Placebo            |  |  |
|--------------------------------------|------------------------------|--------------------|--|--|
| Subject group type                   | Reporting group              | Reporting group    |  |  |
| Number of subjects analysed          | 255 <sup>[7]</sup>           | 253 <sup>[8]</sup> |  |  |
| Units: Days                          |                              |                    |  |  |
| arithmetic mean (standard deviation) | 20.6 (± 10.09)               | 20.2 (± 10.24)     |  |  |

Notes:

[7] - mITT population

[8] - mITT population

## Statistical analyses

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | Number of days on mechanical ventilation |
| Statistical analysis description:  |  |
| Analysis of variance was used to test the null hypothesis of no difference between amikacin inhale and placebo for the number of days on mechanical ventilation. |  |
| Comparison groups  | Amikacin inhale (BAY41-6551) v Placebo   |
| Number of subjects included in analysis  | 508                                      |
| Analysis specification   | Pre-specified                            |
| Analysis type  | superiority                              |
| P-value  | = 0.7144                                 |
| Method   | ANOVA                                    |

### Secondary: Number of days in the ICU through LFU visit

|   |   |
|---|---|
| End point title   | Number of days in the ICU through LFU visit |
| End point description:  |   |
| Number of days in ICU was summarized by descriptive statistics. Duration was defined as the number of days from the date of first study drug through the LFU visit. For subjects who lived in ICU through the LFU visit, the ICU days were actual days in ICU with a maximum value of 28 days. For subjects who died after Day 28 but on or before their LFU visit, the days in ICU was censored at 28 days. For subjects who died or discontinued in ICU, the number of days in ICU was 28 days. Further analysis of the number of days in ICU was to be performed with censoring at Day 28 for subset of subjects on ventilation and without censoring. |   |
| End point type  | Secondary                                   |
| End point timeframe:  |   |
| Up to 28-32 days after start of study treatment   |   |

| End point values                     | Amikacin inhale (BAY41-6551) | Placebo             |  |  |
|--------------------------------------|------------------------------|---------------------|--|--|
| Subject group type                   | Reporting group              | Reporting group     |  |  |
| Number of subjects analysed          | 255 <sup>[9]</sup>           | 253 <sup>[10]</sup> |  |  |
| Units: Days                          |                              |                     |  |  |
| arithmetic mean (standard deviation) | 21.3 (± 8.17)                | 21.9 (± 7.99)       |  |  |

Notes:

[9] - mITT population

[10] - mITT population

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Number of days in the ICU through the LFU visit |
| Statistical analysis description:   |   |
| Analysis of variance was used to test the null hypothesis of no difference between amikacin inhale and placebo for the number of days in the ICU. |   |
| Comparison groups   | Placebo v Amikacin inhale (BAY41-6551)          |

|   |               |
|---|---------------|
| Number of subjects included in analysis | 508           |
| Analysis specification                  | Pre-specified |
| Analysis type                           | superiority   |
| P-value                                 | = 0.4278      |
| Method                                  | ANOVA         |

### Other pre-specified: Per pathogen microbiological response rates at TOC visit

|                 |  |
|-----------------|--|
| End point title | Per pathogen microbiological response rates at TOC visit |
|-----------------|--|

End point description:

The percentage of subjects with microbiological response for each pathogen among the total number of subjects with baseline pathogen isolates for each pathogen was determined. If a subject had 3 pathogens, all 3 were tabulated. Eradication ( defined as the absence of the original pathogen(s) at the post-treatment test-of-cure [TOC] visit culture of specimens from the original site of infection) and presumed eradication (defined as absence of appropriate culture material in a patient judged to be a clinical cure; he or she was unable to produce sputum and invasive procedures were not warranted) rates were reported to reveal the microbiological responses. The data were displayed for each bacterial genus/species. Baseline pathogen was defined as pathogens tested at Screening and Day 1 visit by central laboratory. "99999" denotes that data were not calculated as no subject with baseline pathogen isolates for the specified species in the specified arm.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Up to 17-19 days after start of study treatment

| End point values               | Amikacin inhale (BAY41-6551) | Placebo             |  |  |
|--------------------------------|------------------------------|---------------------|--|--|
| Subject group type             | Reporting group              | Reporting group     |  |  |
| Number of subjects analysed    | 255 <sup>[11]</sup>          | 253 <sup>[12]</sup> |  |  |
| Units: percentage of subjects  |                              |                     |  |  |
| number (not applicable)        |                              |                     |  |  |
| Achromobacter xylosoxidans     | 0                            | 100.0               |  |  |
| Acinetobacter                  | 50.0                         | 99999               |  |  |
| Acinetobacter anitratus        | 59.7                         | 62.3                |  |  |
| Acinetobacter junii            | 100.0                        | 99999               |  |  |
| Burkholderia cepacia complex   | 50.0                         | 50.0                |  |  |
| Chryseobacterium indologenes   | 99999                        | 100.0               |  |  |
| Citrobacter farmeri            | 100.0                        | 99999               |  |  |
| Citrobacter freundii complex   | 75.0                         | 66.7                |  |  |
| Citrobacter koseri             | 42.9                         | 100.0               |  |  |
| Corynebacterium argenteratense | 100.0                        | 99999               |  |  |
| Corynebacterium propinquum     | 99999                        | 0                   |  |  |
| Corynebacterium striatum       | 100.0                        | 0                   |  |  |
| Elizabethkingia meningoseptica | 100.0                        | 100.0               |  |  |
| Enterobacter aerogenes         | 100.0                        | 40.0                |  |  |
| Enterobacter cloacae           | 60.0                         | 62.5                |  |  |
| Enterococcus faecalis          | 100.0                        | 100.0               |  |  |
| Enterococcus faecium           | 100.0                        | 100.0               |  |  |
| Escherichia coli               | 75.0                         | 65.5                |  |  |
| Ewingella americana            | 99999                        | 100.0               |  |  |

|                               |       |       |  |  |
|-------------------------------|-------|-------|--|--|
| Haemophilus influenzae        | 80.0  | 100.0 |  |  |
| Haemophilus parahaemolyticus  | 100.0 | 99999 |  |  |
| Haemophilus parainfluenzae    | 100.0 | 99999 |  |  |
| Hafnia alvei                  | 50.0  | 100.0 |  |  |
| Kerstersia gyiorum            | 100.0 | 0     |  |  |
| Klebsiella oxytoca            | 66.7  | 71.4  |  |  |
| Klebsiella pneumoniae         | 71.7  | 63.6  |  |  |
| Kluyvera intermedia           | 100.0 | 99999 |  |  |
| Moraxella catarrhalis         | 100.0 | 100.0 |  |  |
| Morganella morganii           | 0     | 99999 |  |  |
| Neisseria                     | 100.0 | 0     |  |  |
| Pantoea agglomerans           | 100.0 | 99999 |  |  |
| Pasteurella multocida         | 100.0 | 99999 |  |  |
| Proteus mirabilis             | 66.7  | 60.0  |  |  |
| Proteus vulgaris              | 0     | 99999 |  |  |
| Providencia stuartii          | 99999 | 100.0 |  |  |
| Pseudomonas aeruginosa        | 73.3  | 50.0  |  |  |
| Pseudomonas putida            | 0     | 100.0 |  |  |
| Raoultella ornithinolytica    | 0     | 99999 |  |  |
| Raoultella planticola         | 75    | 66.7  |  |  |
| Serratia liquefaciens         | 100   | 99999 |  |  |
| Serratia marcescens           | 75    | 76.5  |  |  |
| Staphylococcus aureus         | 75    | 66.7  |  |  |
| Staphylococcus haemolyticus   | 100   | 99999 |  |  |
| Stenotrophomonas maltophilia  | 75    | 62.5  |  |  |
| Streptococcus agalactiae      | 100   | 100   |  |  |
| Streptococcus anginosus group | 99999 | 100   |  |  |
| Streptococcus mitis group     | 50    | 0     |  |  |
| Streptococcus pneumoniae      | 100   | 99999 |  |  |

Notes:

[11] - mITT population

[12] - mITT population

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Per subject microbiological response rate at TOC visit

|                 |  |
|-----------------|--|
| End point title | Per subject microbiological response rate at TOC visit |
|-----------------|--|

End point description:

The responses of eradication (defined as the absence of the original pathogen(s) at the post-treatment TOC culture of specimens from the original site of infection) and presumed eradication (defined as absence of appropriate culture material in a subject judged to be a clinical cure; he or she was unable to produce sputum and invasive procedures were not warranted) were tabulated for each subject to reveal the microbiological responses. All pathogen isolates from a subjects must be eradicated (or presumed eradicated) to tabulate an eradicated (or presumed eradicated) response. Baseline pathogen was defined as pathogens tested at Screening and Day 1 visit by central laboratory.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Up to 17-19 days after start of study treatment



| End point values              | Amikacin inhale (BAY41-6551) | Placebo             |  |  |
|-------------------------------|------------------------------|---------------------|--|--|
| Subject group type            | Reporting group              | Reporting group     |  |  |
| Number of subjects analysed   | 255 <sup>[13]</sup>          | 253 <sup>[14]</sup> |  |  |
| Units: Percentage of subjects |                              |                     |  |  |
| number (not applicable)       | 58.8                         | 46.6                |  |  |

Notes:

[13] - mITT population

[14] - mITT population

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Microbiological recurrence rates at LFU visit

|                 |   |
|-----------------|---|
| End point title | Microbiological recurrence rates at LFU visit |
|-----------------|---|

End point description:

The responses of recurrence were tabulated for each subject. Recurrence was defined as the reappearance of the original pathogen(s) from a specimen taken after the TOC visit. If one or more pathogen reappeared, all isolates from a subject were tabulated as "recurrence". Baseline pathogen was defined as pathogens tested at Screening and Day 1 visit by central laboratory.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Up to 28-32 days after start of study treatment

| End point values              | Amikacin inhale (BAY41-6551) | Placebo             |  |  |
|-------------------------------|------------------------------|---------------------|--|--|
| Subject group type            | Reporting group              | Reporting group     |  |  |
| Number of subjects analysed   | 255 <sup>[15]</sup>          | 253 <sup>[16]</sup> |  |  |
| Units: Percentage of subjects |                              |                     |  |  |
| number (not applicable)       | 4.7                          | 4.7                 |  |  |

Notes:

[15] - mITT population

[16] - mITT population

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Emergence of new respiratory pathogens during the aerosol treatment period

|                 |  |
|-----------------|--|
| End point title | Emergence of new respiratory pathogens during the aerosol treatment period |
|-----------------|--|

End point description:

New pathogens also denoted as superinfection was defined as the isolation of a new pathogen (not the original baseline pathogen) from a specimen taken while the subject was on antibiotic therapy (Day 1 to EOT) and having a need for alternative antimicrobial therapy. Rates of emergence of any new pathogen by-subject after start of study drug were summarized for each treatment group.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:  
Up to 10 days after start of study treatment

| End point values              | Amikacin inhale (BAY41-6551) | Placebo             |  |  |
|-------------------------------|------------------------------|---------------------|--|--|
| Subject group type            | Reporting group              | Reporting group     |  |  |
| Number of subjects analysed   | 255 <sup>[17]</sup>          | 253 <sup>[18]</sup> |  |  |
| Units: Percentage of subjects |                              |                     |  |  |
| number (not applicable)       | 8.2                          | 13.4                |  |  |

Notes:

[17] - mITT population

[18] - mITT population

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Emergence of resistance among pathogens by subject

|                 |  |
|-----------------|--|
| End point title | Emergence of resistance among pathogens by subject |
|-----------------|--|

End point description:

Resistance to amikacin was determined for the bacterial isolates by using a standardized microbiology laboratory test that generates a minimum inhibitory concentration (MIC) for amikacin and bacterial isolate. The same microbiology resistance standard was used for all bacteria tested against amikacin. Resistant bacteria have a MIC value of 64 µg/mL or greater. Percentages of resistance were calculated based on the percentage of subjects infected with any treatment-emergent pathogens resistant to amikacin. If a subject had a more than one occurrence of a specific pathogen during pre-treatment period, the worst case of testing was used.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Up to 28-32 days after start of study treatment

| End point values              | Amikacin inhale (BAY41-6551) | Placebo             |  |  |
|-------------------------------|------------------------------|---------------------|--|--|
| Subject group type            | Reporting group              | Reporting group     |  |  |
| Number of subjects analysed   | 186 <sup>[19]</sup>          | 194 <sup>[20]</sup> |  |  |
| Units: Percentage of subjects |                              |                     |  |  |
| number (not applicable)       | 7.0                          | 8.8                 |  |  |

Notes:

[19] - mITT population subjects with pathogen susceptible to amikacin in pre-treatment period

[20] - mITT population subjects with pathogen susceptible to amikacin in pre-treatment period

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Number of subjects who received at least one dose of study drug and reported an adverse event

|  |   |
|--|---|
| End point title  | Number of subjects who received at least one dose of study drug and reported an adverse event |
| End point description:<br>AE was untoward medical occurrence in subject who received study drug without regard to possibility of causal relationship. AEs, occurred any time after the first dose of therapy and through 7 days after the EOT were recorded as treat-emergent AEs (TEAEs). |   |
| End point type   | Other pre-specified   |
| End point timeframe:<br>Up to 7 days after the end of study treatment  |   |

| End point values            | ITT for Safety population - Amikacin inhale | ITT for Safety population - Placebo |  |  |
|-----------------------------|---|-------------------------------------|--|--|
| Subject group type          | Subject analysis set                        | Subject analysis set                |  |  |
| Number of subjects analysed | 353 <sup>[21]</sup>                         | 359 <sup>[22]</sup>                 |  |  |
| Units: Subjects             | 295   | 303                                 |  |  |

Notes:

[21] - ITT for Safety population

[22] - ITT for Safety population

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Number of subjects who received at least one dose of study drug and reported a serious adverse event

|  |  |
|--|--|
| End point title  | Number of subjects who received at least one dose of study drug and reported a serious adverse event |
| End point description:<br>AE was untoward medical occurrence in subject who received study drug without regard to possibility of causal relationship. Serious AE: AE resulting in following outcomes or deemed significant for any reason: death; life-threatening; inpatient hospitalization or prolongation of existing hospitalization; persistent; significant disability/incapacity; congenital anomaly/birth defect; medical important serious event judged by investigator. SAEs, occurred any time after the first dose of therapy and through 7 days after the EOT were recorded as treat-emergent SAEs (TESAEs). |  |
| End point type   | Other pre-specified  |
| End point timeframe:<br>Up to 7 days after the end of study treatment  |  |

| End point values            | ITT for Safety population - Amikacin inhale | ITT for Safety population - Placebo |  |  |
|-----------------------------|---|-------------------------------------|--|--|
| Subject group type          | Subject analysis set                        | Subject analysis set                |  |  |
| Number of subjects analysed | 353 <sup>[23]</sup>                         | 359 <sup>[24]</sup>                 |  |  |
| Units: Subjects             | 101   | 97                                  |  |  |

Notes:

[23] - ITT for Safety population

[24] - ITT for Safety population

## Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Progression and incidence rates of organ failure

|                 |  |
|-----------------|--|
| End point title | Progression and incidence rates of organ failure |
|-----------------|--|

End point description:

The overall percentage of subjects with any organ failure was summarized for each treatment group. Organ failure was defined by a specific organ type and by a collection of MedDRA version 20.0 preferred terms that were determined by the sponsor's clinical team. A subject with multiple AEs within a system organ class or preferred term is counted a single time for that system organ class (SOC) or preferred term.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Up to 7 days after the end of study treatment

| End point values              | ITT for Safety population - Amikacin inhale | ITT for Safety population - Placebo |  |  |
|-------------------------------|---|-------------------------------------|--|--|
| Subject group type            | Subject analysis set                        | Subject analysis set                |  |  |
| Number of subjects analysed   | 353 <sup>[25]</sup>                         | 359 <sup>[26]</sup>                 |  |  |
| Units: Percentage of subjects |   |                                     |  |  |
| number (not applicable)       | 19.5  | 18.7                                |  |  |

Notes:

[25] - ITT for Safety population

[26] - ITT for Safety population

## Statistical analyses

No statistical analyses for this end point

### Other pre-specified: All-cause mortality rate through Day 10 and Day 15

|                 |  |
|-----------------|--|
| End point title | All-cause mortality rate through Day 10 and Day 15 |
|-----------------|--|

End point description:

Number of deaths due to any reason through Day 10 and Day 15 were summarized for each treatment group.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Up to 10 days and 15 days after start of study treatment, respectively

| End point values               | Amikacin inhale (BAY41-6551) | Placebo             |  |  |
|--------------------------------|------------------------------|---------------------|--|--|
| Subject group type             | Reporting group              | Reporting group     |  |  |
| Number of subjects analysed    | 255 <sup>[27]</sup>          | 253 <sup>[28]</sup> |  |  |
| Units: Subjects                |                              |                     |  |  |
| Number of death through Day 10 | 23                           | 32                  |  |  |
| Number of death through Day 15 | 32                           | 39                  |  |  |

---

Notes:

[27] - mITT population

[28] - mITT population

---

### **Statistical analyses**

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

After the first dose of study drug and no later than 7 days after end of treatment

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Patients received 3.2 mL placebo solution aerosolized every 12 hours via PDDS Clinical from Day 1 to Day 10.

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | Amikacin Inhale 400mg q12h |
|-----------------------|----------------------------|

Reporting group description:

Patients received 400 mg (3.2 mL) aerosolized Amikacin (BAY41-6551) solution every 12 hours via PDDS Clinical from Day 1 to Day 10.

| Serious adverse events  | Placebo           | Amikacin Inhale 400mg q12h |  |
|---|-------------------|----------------------------|--|
| Total subjects affected by serious adverse events                   |                   |                            |  |
| subjects affected / exposed   | 97 / 359 (27.02%) | 101 / 353 (28.61%)         |  |
| number of deaths (all causes)                                       | 85                | 86                         |  |
| number of deaths resulting from adverse events                      | 59                | 52                         |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                            |  |
| Acute lymphocytic leukaemia   |                   |                            |  |
| subjects affected / exposed   | 1 / 359 (0.28%)   | 0 / 353 (0.00%)            |  |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 0                      |  |
| deaths causally related to treatment / all                          | 0 / 1             | 0 / 0                      |  |
| Gastric cancer  |                   |                            |  |
| subjects affected / exposed   | 1 / 359 (0.28%)   | 0 / 353 (0.00%)            |  |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 0                      |  |
| deaths causally related to treatment / all                          | 0 / 1             | 0 / 0                      |  |
| Metastases to lung  |                   |                            |  |
| subjects affected / exposed   | 0 / 359 (0.00%)   | 1 / 353 (0.28%)            |  |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 1                      |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0                      |  |
| Vascular disorders  |                   |                            |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| Shock  |                 |                 |  |
| subjects affected / exposed                          | 2 / 359 (0.56%) | 3 / 353 (0.85%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all           | 0 / 2           | 0 / 3           |  |
| Hypotension  |                 |                 |  |
| subjects affected / exposed                          | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Shock haemorrhagic                                   |                 |                 |  |
| subjects affected / exposed                          | 3 / 359 (0.84%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 2           | 0 / 0           |  |
| Deep vein thrombosis                                 |                 |                 |  |
| subjects affected / exposed                          | 2 / 359 (0.56%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Pyrexia  |                 |                 |  |
| subjects affected / exposed                          | 0 / 359 (0.00%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Catheter site haemorrhage                            |                 |                 |  |
| subjects affected / exposed                          | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Multiple organ dysfunction syndrome                  |                 |                 |  |
| subjects affected / exposed                          | 5 / 359 (1.39%) | 5 / 353 (1.42%) |  |
| occurrences causally related to treatment / all      | 0 / 5           | 0 / 5           |  |
| deaths causally related to treatment / all           | 0 / 5           | 0 / 5           |  |
| Respiratory, thoracic and mediastinal disorders      |                 |                 |  |
| Acute respiratory distress syndrome                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 359 (0.28%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Acute respiratory failure                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%) | 2 / 353 (0.57%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Asphyxia  |                 |                 |  |
| subjects affected / exposed                     | 0 / 359 (0.00%) | 2 / 353 (0.57%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atelectasis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 359 (0.00%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchospasm                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 359 (0.00%) | 2 / 353 (0.57%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic obstructive pulmonary disease           |                 |                 |  |
| subjects affected / exposed                     | 3 / 359 (0.84%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Haemothorax                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 359 (0.00%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoxia   |                 |                 |  |
| subjects affected / exposed                     | 2 / 359 (0.56%) | 4 / 353 (1.13%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumothorax                                    |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 359 (0.00%) | 5 / 353 (1.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pneumonia aspiration                            |                 |                 |  |
| subjects affected / exposed                     | 2 / 359 (0.56%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 2 / 359 (0.56%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Pulmonary fibrosis                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Pulmonary oedema                                |                 |                 |  |
| subjects affected / exposed                     | 2 / 359 (0.56%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Respiratory acidosis                            |                 |                 |  |
| subjects affected / exposed                     | 3 / 359 (0.84%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Respiratory failure                             |                 |                 |  |
| subjects affected / exposed                     | 4 / 359 (1.11%) | 9 / 353 (2.55%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 9           |  |
| deaths causally related to treatment / all      | 0 / 3           | 0 / 6           |  |
| Respiratory distress                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 359 (0.00%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sputum retention                                |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Obstructive airways disorder                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 359 (0.00%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Reexpansion pulmonary oedema                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 359 (0.00%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary arterial hypertension                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 359 (0.00%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Bronchial hyperreactivity                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 359 (0.00%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute interstitial pneumonitis                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 359 (0.00%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Psychiatric disorders                           |                 |                 |  |
| Mental status changes                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 359 (0.00%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Product issues                                  |                 |                 |  |
| Device dislocation                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device malfunction                              |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                           | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all       | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| <b>Investigations</b>                                 |                 |                 |  |
| Respiratory rate decreased                            |                 |                 |  |
| subjects affected / exposed                           | 0 / 359 (0.00%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Hepatic enzyme increased                              |                 |                 |  |
| subjects affected / exposed                           | 0 / 359 (0.00%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| <b>Injury, poisoning and procedural complications</b> |                 |                 |  |
| Brain herniation                                      |                 |                 |  |
| subjects affected / exposed                           | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all       | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all            | 0 / 1           | 0 / 0           |  |
| Multiple injuries                                     |                 |                 |  |
| subjects affected / exposed                           | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all       | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all            | 0 / 1           | 0 / 0           |  |
| Pneumonitis chemical                                  |                 |                 |  |
| subjects affected / exposed                           | 0 / 359 (0.00%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Subdural haemorrhage                                  |                 |                 |  |
| subjects affected / exposed                           | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all       | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Anastomotic leak                                      |                 |                 |  |
| subjects affected / exposed                           | 0 / 359 (0.00%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| Post procedural haemorrhage<br>subjects affected / exposed       | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to<br>treatment / all               | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                    | 0 / 0           | 0 / 0           |  |
| Vascular procedure complication<br>subjects affected / exposed   | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to<br>treatment / all               | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                    | 0 / 0           | 0 / 0           |  |
| Gastrointestinal anastomotic leak<br>subjects affected / exposed | 0 / 359 (0.00%) | 1 / 353 (0.28%) |  |
| occurrences causally related to<br>treatment / all               | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                    | 0 / 0           | 0 / 0           |  |
| Weaning failure<br>subjects affected / exposed                   | 2 / 359 (0.56%) | 0 / 353 (0.00%) |  |
| occurrences causally related to<br>treatment / all               | 0 / 2           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                    | 0 / 0           | 0 / 0           |  |
| Cardiac disorders  |                 |                 |  |
| Acute myocardial infarction<br>subjects affected / exposed       | 0 / 359 (0.00%) | 3 / 353 (0.85%) |  |
| occurrences causally related to<br>treatment / all               | 0 / 0           | 0 / 3           |  |
| deaths causally related to<br>treatment / all                    | 0 / 0           | 0 / 2           |  |
| Arrhythmia<br>subjects affected / exposed                        | 0 / 359 (0.00%) | 2 / 353 (0.57%) |  |
| occurrences causally related to<br>treatment / all               | 0 / 0           | 0 / 2           |  |
| deaths causally related to<br>treatment / all                    | 0 / 0           | 0 / 2           |  |
| Atrial fibrillation<br>subjects affected / exposed               | 1 / 359 (0.28%) | 2 / 353 (0.57%) |  |
| occurrences causally related to<br>treatment / all               | 0 / 1           | 0 / 3           |  |
| deaths causally related to<br>treatment / all                    | 0 / 1           | 0 / 0           |  |
| Atrioventricular block complete<br>subjects affected / exposed   | 0 / 359 (0.00%) | 1 / 353 (0.28%) |  |
| occurrences causally related to<br>treatment / all               | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                    | 0 / 0           | 0 / 0           |  |
| Cardiac failure  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 359 (0.56%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| Cardiac arrest                                  |                 |                 |  |
| subjects affected / exposed                     | 3 / 359 (0.84%) | 5 / 353 (1.42%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| Cardiac failure acute                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Cardio-respiratory arrest                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial infarction                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 359 (0.00%) | 2 / 353 (0.57%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cardiogenic shock                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%) | 3 / 353 (0.85%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 3           |  |
| Ventricular arrhythmia                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 359 (0.00%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ventricular tachycardia                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%) | 2 / 353 (0.57%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute left ventricular failure                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 359 (0.00%) | 2 / 353 (0.57%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiovascular insufficiency                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Brain hypoxia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Cerebral ischaemia                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 359 (0.00%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cerebrovascular accident                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 359 (0.00%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhage intracranial                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Haemorrhagic stroke                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 359 (0.00%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Ruptured cerebral aneurysm                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Stroke in evolution                             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 359 (0.00%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| <b>Blood and lymphatic system disorders</b>     |                 |                 |  |
| Anaemia   |                 |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Coagulopathy                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Disseminated intravascular coagulation          |                 |                 |  |
| subjects affected / exposed                     | 0 / 359 (0.00%) | 2 / 353 (0.57%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thrombocytopenia                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Heparin-induced thrombocytopenia                |                 |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Gastrointestinal disorders</b>               |                 |                 |  |
| Gastric ulcer haemorrhage                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 359 (0.00%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Gastrointestinal haemorrhage                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 359 (0.56%) | 2 / 353 (0.57%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Intestinal ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 2 / 359 (0.56%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| Intestinal perforation                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Oesophageal perforation                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis acute                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 359 (0.00%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Upper gastrointestinal haemorrhage              |                 |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Hepatic failure                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Renal failure                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 359 (0.00%) | 2 / 353 (0.57%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 4 / 359 (1.11%) | 5 / 353 (1.42%) |  |
| occurrences causally related to treatment / all | 2 / 4           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Muscle haemorrhage                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Bacteraemia                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%) | 3 / 353 (0.85%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchopulmonary aspergillosis                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 359 (0.00%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Lung abscess                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 359 (0.00%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Infection                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 359 (0.00%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Mediastinitis                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 359 (0.00%) | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pathogen resistance                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peritonitis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%) | 2 / 353 (0.57%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| Pneumonia                                       |                  |                 |  |
| subjects affected / exposed                     | 5 / 359 (1.39%)  | 5 / 353 (1.42%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 4           |  |
| Postoperative wound infection                   |                  |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%)  | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pneumonia pseudomonal                           |                  |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%)  | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Sepsis  |                  |                 |  |
| subjects affected / exposed                     | 4 / 359 (1.11%)  | 5 / 353 (1.42%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 3           |  |
| Septic shock                                    |                  |                 |  |
| subjects affected / exposed                     | 15 / 359 (4.18%) | 7 / 353 (1.98%) |  |
| occurrences causally related to treatment / all | 0 / 15           | 0 / 7           |  |
| deaths causally related to treatment / all      | 0 / 14           | 0 / 6           |  |
| Urosepsis                                       |                  |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%)  | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Pulmonary sepsis                                |                  |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%)  | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Lung infection                                  |                  |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%)  | 1 / 353 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1           |  |
| Device related sepsis                           |                  |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bacillus bacteraemia                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 359 (0.28%) | 0 / 353 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Failure to thrive                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 359 (0.00%) | 2 / 353 (0.57%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2           |  |

Frequency threshold for reporting non-serious adverse events: 2 %

| <b>Non-serious adverse events</b>                     | Placebo            | Amikacin Inhale<br>400mg q12h |  |
|---|--------------------|-------------------------------|--|
| Total subjects affected by non-serious adverse events |                    |                               |  |
| subjects affected / exposed                           | 214 / 359 (59.61%) | 207 / 353 (58.64%)            |  |
| Vascular disorders                                    |                    |                               |  |
| Hypertension  |                    |                               |  |
| subjects affected / exposed                           | 7 / 359 (1.95%)    | 13 / 353 (3.68%)              |  |
| occurrences (all)                                     | 8                  | 13                            |  |
| Hypotension   |                    |                               |  |
| subjects affected / exposed                           | 12 / 359 (3.34%)   | 23 / 353 (6.52%)              |  |
| occurrences (all)                                     | 12                 | 24                            |  |
| Deep vein thrombosis                                  |                    |                               |  |
| subjects affected / exposed                           | 3 / 359 (0.84%)    | 9 / 353 (2.55%)               |  |
| occurrences (all)                                     | 3                  | 9                             |  |
| General disorders and administration site conditions  |                    |                               |  |
| Oedema  |                    |                               |  |
| subjects affected / exposed                           | 9 / 359 (2.51%)    | 5 / 353 (1.42%)               |  |
| occurrences (all)                                     | 9                  | 5                             |  |
| Oedema peripheral                                     |                    |                               |  |
| subjects affected / exposed                           | 13 / 359 (3.62%)   | 9 / 353 (2.55%)               |  |
| occurrences (all)                                     | 14                 | 12                            |  |

|  |  |  |  |
|--|--|--|--|
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)  | 21 / 359 (5.85%)<br>24   | 18 / 353 (5.10%)<br>21   |  |
| Respiratory, thoracic and mediastinal disorders<br>Bronchospasm<br>subjects affected / exposed<br>occurrences (all)<br><br>Dyspnoea<br>subjects affected / exposed<br>occurrences (all)  | 2 / 359 (0.56%)<br>2<br><br>9 / 359 (2.51%)<br>9                                 | 10 / 353 (2.83%)<br>15<br><br>7 / 353 (1.98%)<br>9                             |  |
| Psychiatric disorders<br>Delirium<br>subjects affected / exposed<br>occurrences (all)<br><br>Agitation<br>subjects affected / exposed<br>occurrences (all)<br><br>Insomnia<br>subjects affected / exposed<br>occurrences (all) | 9 / 359 (2.51%)<br>9<br><br>12 / 359 (3.34%)<br>12<br><br>11 / 359 (3.06%)<br>11 | 14 / 353 (3.97%)<br>15<br><br>8 / 353 (2.27%)<br>8<br><br>6 / 353 (1.70%)<br>6 |  |
| Investigations<br>Oxygen saturation decreased<br>subjects affected / exposed<br>occurrences (all)  | 8 / 359 (2.23%)<br>10  | 5 / 353 (1.42%)<br>5   |  |
| Cardiac disorders<br>Atrial fibrillation<br>subjects affected / exposed<br>occurrences (all)<br><br>Tachycardia<br>subjects affected / exposed<br>occurrences (all)  | 10 / 359 (2.79%)<br>10<br><br>11 / 359 (3.06%)<br>11                             | 9 / 353 (2.55%)<br>9<br><br>6 / 353 (1.70%)<br>6                               |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)<br><br>Coagulopathy  | 44 / 359 (12.26%)<br>49  | 36 / 353 (10.20%)<br>38  |  |

|  |                        |                      |  |
|--|------------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all) | 10 / 359 (2.79%)<br>11 | 5 / 353 (1.42%)<br>5 |  |
| Gastrointestinal disorders                       |                        |                      |  |
| Constipation                                     |                        |                      |  |
| subjects affected / exposed                      | 32 / 359 (8.91%)       | 30 / 353 (8.50%)     |  |
| occurrences (all)                                | 32                     | 30                   |  |
| Diarrhoea  |                        |                      |  |
| subjects affected / exposed                      | 33 / 359 (9.19%)       | 27 / 353 (7.65%)     |  |
| occurrences (all)                                | 34                     | 30                   |  |
| Gastrointestinal haemorrhage                     |                        |                      |  |
| subjects affected / exposed                      | 6 / 359 (1.67%)        | 13 / 353 (3.68%)     |  |
| occurrences (all)                                | 6                      | 13                   |  |
| Vomiting   |                        |                      |  |
| subjects affected / exposed                      | 17 / 359 (4.74%)       | 6 / 353 (1.70%)      |  |
| occurrences (all)                                | 18                     | 7                    |  |
| Hepatobiliary disorders                          |                        |                      |  |
| Hepatic function abnormal                        |                        |                      |  |
| subjects affected / exposed                      | 13 / 359 (3.62%)       | 12 / 353 (3.40%)     |  |
| occurrences (all)                                | 13                     | 12                   |  |
| Skin and subcutaneous tissue disorders           |                        |                      |  |
| Decubitus ulcer                                  |                        |                      |  |
| subjects affected / exposed                      | 14 / 359 (3.90%)       | 11 / 353 (3.12%)     |  |
| occurrences (all)                                | 14                     | 11                   |  |
| Renal and urinary disorders                      |                        |                      |  |
| Oliguria   |                        |                      |  |
| subjects affected / exposed                      | 8 / 359 (2.23%)        | 3 / 353 (0.85%)      |  |
| occurrences (all)                                | 8                      | 3                    |  |
| Renal impairment                                 |                        |                      |  |
| subjects affected / exposed                      | 9 / 359 (2.51%)        | 4 / 353 (1.13%)      |  |
| occurrences (all)                                | 9                      | 4                    |  |
| Acute kidney injury                              |                        |                      |  |
| subjects affected / exposed                      | 7 / 359 (1.95%)        | 9 / 353 (2.55%)      |  |
| occurrences (all)                                | 9                      | 9                    |  |
| Infections and infestations                      |                        |                      |  |
| Septic shock                                     |                        |                      |  |
| subjects affected / exposed                      | 5 / 359 (1.39%)        | 8 / 353 (2.27%)      |  |
| occurrences (all)                                | 5                      | 11                   |  |

|   |                         |                        |  |
|---|-------------------------|------------------------|--|
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | 10 / 359 (2.79%)<br>10  | 10 / 353 (2.83%)<br>11 |  |
| Metabolism and nutrition disorders  |                         |                        |  |
| Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all)           | 10 / 359 (2.79%)<br>10  | 14 / 353 (3.97%)<br>14 |  |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)          | 10 / 359 (2.79%)<br>11  | 8 / 353 (2.27%)<br>8   |  |
| Hypoglycaemia<br>subjects affected / exposed<br>occurrences (all)           | 9 / 359 (2.51%)<br>12   | 5 / 353 (1.42%)<br>5   |  |
| Hypernatraemia<br>subjects affected / exposed<br>occurrences (all)          | 12 / 359 (3.34%)<br>12  | 9 / 353 (2.55%)<br>9   |  |
| Hypomagnesaemia<br>subjects affected / exposed<br>occurrences (all)         | 7 / 359 (1.95%)<br>7    | 8 / 353 (2.27%)<br>9   |  |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)            | 37 / 359 (10.31%)<br>40 | 32 / 353 (9.07%)<br>36 |  |
| Hypophosphataemia<br>subjects affected / exposed<br>occurrences (all)       | 11 / 359 (3.06%)<br>11  | 6 / 353 (1.70%)<br>6   |  |
| Hyponatraemia<br>subjects affected / exposed<br>occurrences (all)           | 12 / 359 (3.34%)<br>12  | 17 / 353 (4.82%)<br>17 |  |
| Hypoproteinaemia<br>subjects affected / exposed<br>occurrences (all)        | 4 / 359 (1.11%)<br>4    | 8 / 353 (2.27%)<br>9   |  |
| Metabolic alkalosis<br>subjects affected / exposed<br>occurrences (all)     | 10 / 359 (2.79%)<br>10  | 8 / 353 (2.27%)<br>10  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date           | Amendment  |
|----------------|--|
| 18 July 2016   | <p>To shorten the time required to obtain the data from the two Phase 3 clinical studies of the Amikacin Inhale program (BAY 41 6551/13084 [Inhale I] and BAY 41-6551/13085 [Inhale II]) to sustain regulatory submission, the Sponsor, Bayer AG, decided that the results of both studies should be consolidated into a single integrated report.</p> <p>As there will be no second study to corroborate the findings in the consolidated report it was considered necessary to review the endpoints to ensure optimal clinical relevance. During a blinded review of the data from 106 patients entered into the Phase 3 program it was found that there was an artificially high failure rate occasioned by the original antibiotic use rules.</p> <p>These failures did not correspond with data that are used as medical management tools and were considered spurious. Certain other elements of the original endpoint were also considered not to accurately reflect clinical benefit. This required modifications a priori of the statistical analysis plan, but did not require any alterations to patient management, modifications to data collection tools, or changes to clinical/laboratory evaluations being performed at the ICU to assess Clinical Failure or Success. The aim was that the patient population recruited into the study and the management of the patients would be the same after the implementation of this amendment as it was before.</p> <p>Recruitment continued in the two studies until a total of approximately 724 patients had been enrolled. Enrollment was competitive and both studies were planned to stop once the number was reached.</p> <p>The primary efficacy endpoint had been modified to allow antibiotic rules to better reflect Clinical Success or Failure and the other variables to be more clearly aligned with clinical response. The secondary variables, Days in hospital and relapses rates were removed, pneumonia-related mortality added and speed of response based on CPIS success or failure added.</p> |
| 30 August 2016 | <p>A correction was made in the temperature criterion for the calculation of CPIS points. This correction accurately reflects the programming that has been used in the electronic case report form by the investigators to calculate the CPIS score throughout the study, i.e., it did not represent a change in the conduct of the study. Note: This was an error in the original protocol that was carried forward in other amendments.</p>   |
| 07 April 2017  | <p>The amendment date was 29-Aug-2017. During a blinded review of the data from 454 mITT patients entered into the Phase III program it was found that there was an artificially high failure rate due to the antibiotic criteria. These failures did not correspond with data that are used as medical management tools and were considered spurious. Certain other elements of the endpoint related to the TOC date were also considered not to accurately reflect clinical benefit.</p> <p>These data necessitated a change in the primary endpoint. It was decided to narrow the primary endpoint to all-cause mortality alone through the LFU visit (Days 28-32).</p> <p>This primary endpoint is in alignment with current FDA draft guidance for ventilated pneumonia. All-cause mortality through the LFU visit was the sole criterion for evaluation. Survival was the new primary endpoint.</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.

To shorten the time required to obtain data from the 2 clinical studies of Amikacin Inhale Phase 3 program, Bayer and the FDA decided that the results of studies NCT01799993 and NCT00805168 should be consolidated into a single report.

Notes: