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	2013-001048-73
Trial protocol	CZ
Global end of trial date	07 April 2017

Results information

Result version number	v1
This version publication date	12 April 2018
First version publication date	12 April 2018

Trial information

Trial identification

Sponsor protocol code	BAY41-6551/13084

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:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	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
Arm title	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.

Arm title	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.

Number of subjects in period 1	Amikacin inhale (BAY41-6551)	Placebo
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 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 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:	
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 ≥ 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:	
Included all subjects in ITT anlaysis 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:	
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:	
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:	
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:	
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 Units: Subjects			
<18 18 to <45 18 to <65 65 to <75 >= 75			
Age continuous Units: years arithmetic mean standard deviation	±	±	±
Gender categorical Units: Subjects			
Female Male			
Ethnicity 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:	
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:	
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:	
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:	
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 ≥ 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:	
Included all subjects in ITT anlaysis 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:	
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:	
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:	
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:	
Included all subject in ITT analysis set who were treated with placebo	

Primary: Survival through LFU visit

End point title	Survival through LFU visit
End point description:	
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:	
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[1]	253[2]		
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-Haenzel (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	Amikacin inhale (BAY41-6551) v Placebo
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[3]	57[4]		
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[5]	253[6]		
Units: Subjects				
Early Clinical Response - Success	149	145		
Early Clinical Response - Failure	106	108		

Notes:

[5] - mITT population

[6] - mITT population

Statistical analyses

Statistical analysis title	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

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

Notes:

[7] - mITT population

[8] - mITT population

Statistical analyses

Statistical analysis title	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[9]	253[10]		
Units: Days				
arithmetic mean (standard deviation)	21.3 (± 8.17)	21.9 (± 7.99)		

Notes:

[9] - mITT population

[10] - mITT population

Statistical analyses

Statistical analysis title	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[11]	253[12]		
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 argentoratense	100.0	99999		
Corynebacterium propinquum	99999	0		
Corynebacterium striatum	100.0	0		
Elizabethkingia meningoceptica	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[13]	253[14]		
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[15]	253[16]		
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[17]	253[18]		
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[19]	194[20]		
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:

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:

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[21]	359[22]		
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:

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:

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[23]	359[24]		
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[25]	359[26]		
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[27]	253[28]		
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			

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			
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	
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	
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	
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	
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 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	
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	
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	
Investigations			
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	
Injury, poisoning and procedural complications			
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			
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	
Vascular procedure complication			
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	
Gastrointestinal 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	
Weaning failure			
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	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 359 (0.00%)	3 / 353 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Arrhythmia			
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	
Atrial fibrillation			
subjects affected / exposed	1 / 359 (0.28%)	2 / 353 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrioventricular block complete			
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	
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			
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 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	
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	
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	
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	
Blood and lymphatic system disorders			
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	
Gastrointestinal disorders			
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	
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	
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	
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	
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	
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	
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 %

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 July 2016	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. 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. 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. 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. 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.
30 August 2016	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.
07 April 2017	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. 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). 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.

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: