# Inhaled amikacin adjunctive to intravenous standard-of-care antibiotics in mechanically ventilated patients with Gram-negative pneumonia (INHALE): a double-blind, randomised, placebo-controlled, phase 3, superiority trial

*Michael S Niederman, Jeff Alder, Matteo Bassetti, Francis Boateng, Bin Cao, Kevin Corkery, Rajiv Dhand, Keith S Kaye, Robert Lawatscheck, Patrick McLeroth, David P Nicolau, Chen Wang, G Christopher Wood, Richard G Wunderink, Jean Chastre*

## Summary

**Background** Treatment of ventilated pneumonia is often unsuccessful, even when patients are treated according to established guidelines. Therefore, we aimed to investigate the efficacy of the combination drug device Amikacin Inhale as an adjunctive therapy to intravenous standard-of-care antibiotics for pneumonia caused by Gram-negative pathogens in intubated and mechanically ventilated patients.

**Methods** INHALE was a prospective, double-blind, randomised, placebo-controlled, phase 3 study comprising two trials (INHALE 1 and INHALE 2) done in 153 hospital intensive-care units in 25 countries. Eligible patients were aged 18 years or older; had pneumonia that had been diagnosed by chest radiography and that was documented as being caused by or showing two risk factors for a Gram-negative, multidrug-resistant pathogen; were intubated and mechanically ventilated; had impaired oxygenation within 48 h before screening; and had a modified Clinical Pulmonary Infection Score of at least 6. Patients were stratified by region and disease severity (according to their Acute Physiology and Chronic Health Evaluation [APACHE] II score) and randomly assigned (1:1) via an interactive voice-recognition system to receive 400 mg amikacin (Amikacin Inhale) or saline placebo, both of which were aerosolised, administered every 12 h for 10 days via the same synchronised inhalation system, and given alongside standard-of-care intravenous antibiotics. All patients and all staff involved in administering devices and monitoring outcomes were masked to treatment assignment. The primary endpoint, survival at days 28–32, was analysed in all patients who received at least one dose of study drug, were infected with a Gram-negative pathogen, and had an APACHE II score of at least 10 at diagnosis. Safety analyses were done in all patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, numbers NCT01799993 and NCT00805168.

**Findings** Between April 13, 2013, and April 7, 2017, 807 patients were assessed for eligibility and 725 were randomly assigned to Amikacin Inhale (362 patients) or aerosolised placebo (363 patients). 712 patients received at least one dose of study drug (354 in the Amikacin Inhale group and 358 in the placebo group), although one patient assigned to Amikacin Inhale received placebo in error and was included in the placebo group for safety analyses. 508 patients (255 in the Amikacin Inhale group and 253 in the placebo group) were assessed for the primary endpoint. We found no between-group difference in survival: 191 (75%) patients in the Amikacin Inhale group versus 196 (77%) patients in the placebo group survived until days 28–32 (odds ratio 0·841, 95% CI 0·554–1·277; p=0·43). Similar proportions of patients in the two treatment groups had a treatment-emergent adverse event (295 [84%] of 353 patients in the Amikacin Inhale group *vs* 303 [84%] of 359 patients in the placebo group) or a serious treatment-emergent adverse event (101 [29%] patients *vs* 97 [27%] patients).

**Interpretation** Our findings do not support use of inhaled amikacin adjunctive to standard-of-care intravenous therapy in mechanically ventilated patients with Gram-negative pneumonia.

**Funding** Bayer AG.



## Introduction

Hospital-acquired pneumonia and ventilator-associated pneumonia are common infections in intensive care units (ICUs), causing a high burden of disease and mortality.[1,2] In a 17-year, US epidemiological study sample of more than 8 million mechanically ventilated patients, pneumonia was associated with mortality in 34–44% of patients.[3] All-cause mortality in patients with ventilator-associated pneumonia is 20–50%, and an estimated 13% of deaths in these patients are attributable to pneumonia.[2] European and US guidelines, which include use of empirical antimicrobial therapy, were established for the initial management of ventilator-associated pneumonia, hospital-acquired pneumonia, health care-associated pneumonia,

*Lancet Infect Dis* 2019

Published Online December 19, 2019 https://doi.org/10.1016/S1473-3099(19)30574-2

See Online/Comment https://doi.org/10.1016/S1473-3099(19)30690-5

**Division of Pulmonary and Critical Care Medicine, New York Presbyterian/Weill Cornell Medical Center, New York, NY, USA** (Prof M S Niederman MD); **Anti-Infective Consulting, Margaretville, NY, USA** (J Alder PhD); **Infectious Diseases Clinic, Department of Health Sciences, University of Genoa and Policlinico San Martino Hospital, Genoa, Italy** (Prof M Bassetti MD); **Department of Health Sciences, University of Genoa, Genoa, Italy** (Prof M Bassetti); **Bayer Healthcare Inc, Whippany, NJ, USA** (F Boateng PhD); **Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital, Beijing, China** (Prof B Cao MD, Prof C Wang MD); **Novartis Pharmaceuticals, San Carlos, CA, USA** (K Corkery BSc); **Department of Medicine, University of Tennessee Graduate School of Medicine, Knoxville, TN, USA** (Prof R Dhand MD); **Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI, USA** (Prof K S Kaye MD); **Bayer AG, Berlin, Germany** (R Lawatscheck MD); **Covance, Princeton, NJ, USA** (P McLeroth MD); **Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, CT, USA** (D P Nicolau PharmD); **Department of Clinical Pharmacy and Translational Science, University of Tennessee Health Science**

**Center, University of Tennessee, Memphis, TN, USA** (Prof G C Wood PharmD); **Division of Pulmonary and Critical Care Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA** (Prof R G Wunderink MD); **and Intensive Care Unit, Sorbonne University Hospitals, Paris, France** (Prof J Chastre MD)

Correspondence to: Prof Michael S Niederman, Division of Pulmonary and Critical Care Medicine, Weill Cornell Medicine, New York, NY 10065, USA
**msn9004@med.cornell.edu**

## Research in context

### Evidence before this study

Before the INHALE study began, to our knowledge, there were no published reports of prospective studies of the clinical efficacy of aerosolised amikacin, used adjunctive to intravenous standard-of-care antibiotic therapy, in patients with ventilator-associated or hospital-acquired Gram-negative pneumonia. Mixed results had been reported from investigations of nebulised colistin adjunctive to intravenous therapy in these patients. We searched PubMed, without any language restrictions, for studies published between Jan 1, 1970, and July 31, 2018, using the search terms "pneumonia AND Gram-negative AND ventilat* AND amikacin AND (aerosol OR nebul*)". We found one published report of a randomised, placebo-controlled phase 2 study and three reports of pharmacokinetic studies of Amikacin Inhale. We also found a retrospective chart review of 49 critically ill patients with episodes of ventilator-associated pneumonia, nine episodes of which had been treated with nebulised amikacin. The dosing regimen of amikacin used in our study was based on findings from the phase 2 study, which showed that amikacin accumulated in tracheal aspirates at concentrations that were considerably greater than the minimum inhibitory concentrations of relevant Gram-negative pathogens. The pharmacokinetic studies confirmed that aerosolised delivery by this synchronised method yielded much higher concentrations of amikacin in tracheal aspirates than in plasma, even in patients with reduced kidney function.

### Added value of this study

In a large patient population, we found no survival benefit associated with aerosolised amikacin compared with placebo, when administered adjunctively to intravenous standard-of-care antibiotic therapy in critically ill patients with suspected or confirmed multidrug-resistant, ventilator-associated, Gram-negative pneumonia. These findings corroborate those from the phase 2 IASIS trial in a similar patient population that showed no improvement in Clinical Pulmonary Infection Scores with nebulised amikacin plus fosfomycin compared with placebo, when administered adjunctively to intravenous standard-of-care antibiotics.

### Implications of all the available evidence

Taken together, the findings from INHALE and IASIS suggest there is no survival benefit associated with the use of aerosolised amikacin adjunctive to intravenous antibiotics in patients with drug-resistant, ventilator-associated, Gram-negative pneumonia. Current pneumonia treatment guidelines recommend the adjunctive use of inhaled antibiotics as rescue therapy and in patients with drug-resistant infections susceptible only to aminoglycosides and polymyxins. Prospective controlled trials might be warranted to determine whether inhaled antibiotics have demonstrable benefit in these circumstances.

and community-acquired pneumonia.[1,2,4,5] Even when patients are treated according to these guidelines and with standard-of-care systemic intravenous antibiotics, the frequency of clinical success is variable, occurring in 36–69% of patients in clinical trials.[6–9]

Suboptimal outcomes are among the key challenges of delivering effective concentrations of antibiotics to the site of lung infection in critically ill patients. Hospital-acquired pneumonia and ventilator-associated pneumonia can be caused by difficult-to-treat pathogens, and altered physiology in critically ill patients can adversely affect antibiotic pharmacokinetics.[2,10,11] Treatment can be unsuccessful if the alveolar concentrations of antibiotics that are needed to kill pathogens in the lungs are not achieved after intravenous administration,[12] and safety concerns (such as neurotoxicity with β-lactams or ototoxicity and nephrotoxicity with aminoglycosides)[2,12–14] prevent increased systemic dosing of some antibiotics to attain the alveolar concentrations required.[15,16]

Targeting the lungs with inhaled antibiotic therapy could address these issues by achieving high alveolar concentrations of antibiotics while minimising systemic exposure.[16,17] Although not yet approved by the US Food and Drug Administration (FDA),[12,16] clinical practice guidelines[2] from 2016 support treatment with inhaled antibiotics when used adjunctively with systemic antibiotics (rather than systemic antibiotics alone) in patients with ventilator-associated pneumonia caused by Gram-negative bacilli that are susceptible to only aminoglycosides or polymyxins. If the patient is not responding to intravenous antibiotics alone, adjunctive inhaled antibiotics can also be considered as a last resort, irrespective of whether the pathogen is multidrug-resistant.[2] However, to our knowledge, no large randomised, placebo-controlled, phase 3 clinical trial has assessed the effectiveness of inhaled antibiotics, and results from smaller studies are inconclusive.[16,18–22] Evidence from large, well controlled clinical trials is, therefore, urgently needed.[2,18,19,22]

Off-label, aerosolised antibiotic therapy uses generic intravenous antibiotic solutions and inhalation devices. Such non-standardised and largely untested methods can result in suboptimal lung deposition, with associated uncertainties about efficacy and safety.[18,19,23–25] Amikacin Inhale (Bayer AG, Berlin, Germany) is an integrated drug-device product that was designed to achieve high amikacin concentrations in the lungs while maintaining low systemic exposure[26–28] and to minimise the potential for poor or inconsistent antibiotic delivery, which have been associated with inhaled antibiotic administration by other devices.[25] The drug component of Amikacin Inhale, amikacin inhalation solution (Bayer AG, Berlin, Germany), is a preservative-free formulation that is pH-adjusted to reduce the risk of bronchospasm.[26]

In a phase 1 study, the median amikacin concentration in epithelial lining fluid 30 min after dosing with Amikacin Inhale was 976 µg/mL (range 136–16 128). This concentration is more than ten times the minimum inhibitory concentration for *Pseudomonas aeruginosa* (8 µg/mL).[26] In a phase 2 study, 50% of mechanically ventilated patients with Gram-negative pneumonia fulfilled the study's composite endpoint, achieving on day 1 a maximum amikacin concentration in tracheal aspirates of at least 6400 µg/mL (which is at least 25 times greater than a reference minimum inhibitory concentration for hospital-acquired organisms) and an area under the concentration–time curve in tracheal aspirates that was at least 100 times greater than the reference minimum inhibitory concentration.[27] Accordingly, the dose used in the phase 2 study (400 mg, twice daily) was chosen for our study.

The INHALE study aimed to assess whether Amikacin Inhale, in combination with intravenous standard-of-care, is superior to aerosolised placebo with intravenous standard-of-care for treatment of Gram-negative pneumonia in intubated and mechanically ventilated adults, with the aim of reducing mortality. The design of our study permitted evaluation of inhaled antibiotics as a first-line adjunctive therapy (as opposed to rescue therapy), when Gram-negative infection is likely but not necessarily proven.[2]

## Methods

### Study design and participants

INHALE was a prospective, double-blind, randomised, placebo-controlled, phase 3 study that consolidated two trials: INHALE 1 (ClinicalTrials.gov, number NCT01799993) and INHALE 2 (ClinicalTrials.gov, number NCT00805168). The protocols of these trials were identical, except that INHALE 2 included a pharmacokinetic subgroup. Pharmacokinetic data are reported in the appendix (pp 10, 18). The trials were done in 153 hospital ICUs in 25 countries. Participating regions included the USA, Europe, South America, and Asia (appendix pp 1–4), and all attending staff at all centres were given device training. Additional details on the study design are shown in the appendix (p 19).

Patients were eligible for study inclusion if they were aged 18 years or older; had pneumonia that had been diagnosed by chest radiography and that was documented as being caused by, or showing two risk factors (appendix p 5) for, a Gram-negative, multidrug-resistant pathogen (appendix pp 6–7, 11); were intubated and mechanically ventilated (including via tracheostomy); had impaired oxygenation (partial pressure of arterial oxygen/fractional concentration of oxygen in inspired air ≤300 mm Hg) within 48 h before screening; and had a modified Clinical Pulmonary Infection Score (CPIS) of at least 6 (maximum score of 10; appendix p 12). Participants were excluded if they had received systemic antibiotic treatment for Gram-negative pneumonia for more than 48 h before the study drug was administered, unless the infection was resistant to the antibiotic used or the patient's pneumonia was worsening. Full eligibility criteria are shown in the appendix (pp 5–6).

Patients, or their legally authorised representative, gave written informed consent for study participation. Our study was done in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki.[29,30] The protocol (appendix pp 23–227) and all amendments were approved by each site's institutional review board or independent ethics committee and by the FDA.

### Randomisation and masking

Patients were stratified by region and disease severity (according to their Acute Physiology and Chronic Health Evaluation [APACHE] II score) and randomly assigned (1:1) to Amikacin Inhale or placebo groups. The sponsor (Bayer AG) generated randomisation codes, and patients were allocated to treatment by an interactive voice-recognition system. All patients and all staff involved in administering devices and monitoring outcomes were masked to treatment assignment. Study drugs were supplied in brown glass vials to prevent patients and study personnel from knowing treatment assignments. As part of routine management, serum amikacin concentrations were determined and reported to attending physicians according to institutional guidelines, at the order of the managing clinician and only if patients were receiving intravenous amikacin.

### Procedures

Adjunctive to standard-of-care intravenous antibiotics, patients received aerosolised study drug administered by trained ICU staff every 12 h for 10 days via a synchronised inhalation system. Study drug was either amikacin inhalation solution (400 mg amikacin in 3·2 mL saline) or placebo (3·2 mL saline). Both treatments were aerosolised and administered via a synchronised inhalation system (appendix p 20). Patients who were extubated before day 10 (the end-of-therapy [EOT] visit) completed therapy under staff supervision using a self-administered handheld nebuliser plus spacer chamber that shared design elements with the synchronised inhalation device (appendix p 21). To be eligible for inclusion in the study, patients could have received standard-of-care intravenous antibiotics for Gram-negative pneumonia up to 48 h before the aerosolised study drug, and antibiotic treatment was continued at least until the EOT visit. After this time, the duration of intravenous antibiotics was decided by the primary-service clinician or based on pathogen-specific treatment criteria mandated by the treating institution. Investigators and primary-service clinicians also selected the therapy for standard-of-care intravenous antibiotic treatment on the basis of local guidelines and local Gram-negative multidrug-resistant patterns. Standard of care typically included two antibiotics recommended by the American Thoracic Society/Infectious Diseases Society of

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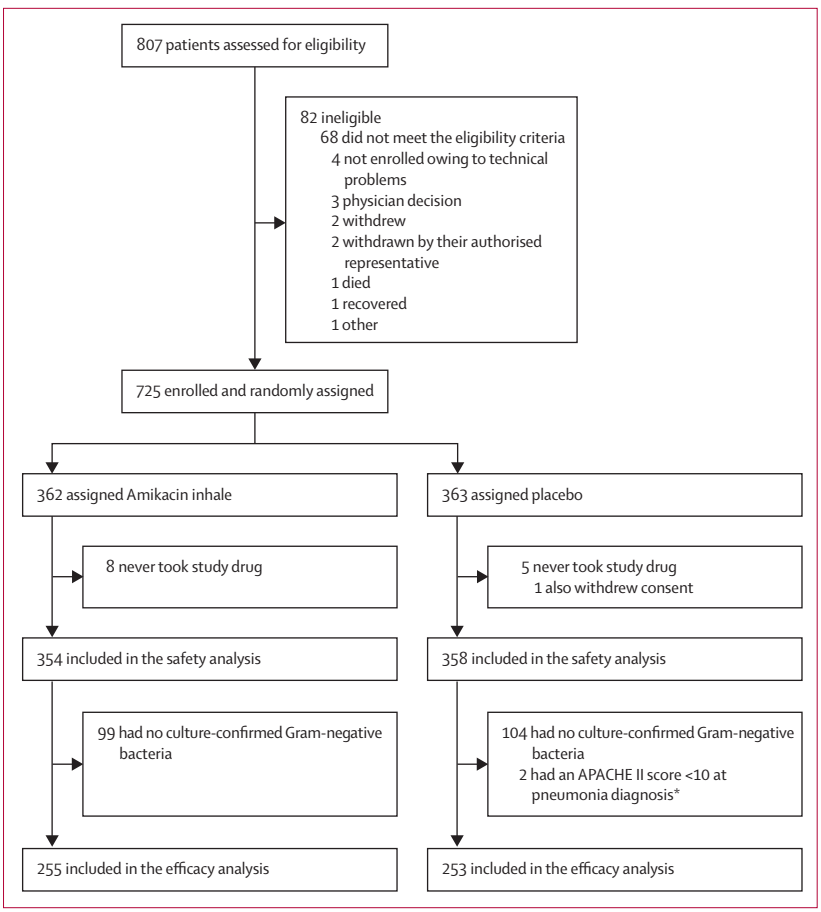


***Figure 1:*** **Patient disposition**
Patients were given 400 mg aerosolised amikacin or aerosolised placebo twice a day, as well as standard-of-care intravenous antibiotics. APACHE=Acute Physiology and Chronic Health Evaluation. *One of these patients also had no culture-confirmed Gram-negative bacteria.

America guidelines.[4] If the investigator selected a systemic aminoglycoside, the protocol specified use of amikacin. Thus, monitoring for supratherapeutic aminoglycoside concentrations in serum could be undertaken without unmasking study treatment assignments.

Study assessments (appendix p 13) were done at screening (the 48-h period before starting therapy), on days 1, 3, 5, 7, and 10 (the EOT visit); days 17–19 (the test-of-cure visit); and days 28–32 (the late follow-up [LFU] visit; appendix p 19). Chest x-rays and respiratory samples were obtained at each timepoint, when clinically indicated by signs of infection worsening or resolution. Pleural fluid cultures were obtained as determined by the clinician from patients with evidence of pleural effusion, or if otherwise indicated. Patients who discontinued therapy prematurely received safety assessments until the LFU visit.

## Outcomes

The primary efficacy endpoint was survival until the LFU visit; no factors other than treatment assignment were considered in evaluating survival. A prespecified supporting analysis of survival was also done in the safety population. If the primary endpoint was met, we planned to assess secondary efficacy endpoints in the following order, evaluation of each being dependent on the preceding endpoint being met: pneumonia-related mortality until LFU visit; early clinical response; number of days on mechanical ventilation until LFU visit; and number of days spent in the ICU, assessed at LFU visit. Pneumonia-related mortality was determined by a masked adjudication committee. Early clinical response was a composite endpoint based on CPIS (appendix p 12) on days 3, 5, and 10 (*vs* baseline CPIS); the presence of empyema or or lung abscess at days 3, 5, or 10; and all-cause mortality up to the EOT visit. Early clinical response was considered to have been attained if success criteria for all three CPIS determinations were met (appendix p 7), and if patients had not died or developed empyema or lung abscesses. Patients who withdrew consent were considered to have been unsuccessfully treated unless all outcome data were available for the primary analysis and the patient consented to their data being used. Treatment was also classified as unsuccessful if it was discontinued because of an adverse event, death, implementation of treatment that was incompatible with aerosol therapy, or loss to follow-up. If a patient died, their time on mechanical ventilation and in the ICU was censored at 28 days.

As safety assessments, we evaluated treatment-emergent adverse events (TEAEs; ie, those occurring at any time after the first dose of study drug and within 7 days of the EOT visit), serious TEAEs (ie, TEAEs occurring within 28 days of the EOT visit), and TEAEs of special interest, based on sponsor-defined MedDRA preferred terms. The severity of TEAEs was graded as mild (usually transient in nature and generally not interfering with normal activities), moderate (sufficiently discomforting to interfere with normal activities), or severe (preventing normal activities). Additional details on the secondary, exploratory, and safety endpoints are shown in the appendix (pp 7–9).

We did post-hoc subgroup analyses of the primary endpoint (appendix p 10), based on the duration of treatment with intravenous antibiotics before initiation of study drug (0–48 h *vs* >48 h); duration of standard-of-care intravenous antibiotics (therapy stopped at or before the EOT visit *vs* therapy stopped after the EOT visit); the occurrence of septic shock; geographical region; and the drug resistance designation of the infecting pathogen (not multidrug-resistant [ie, resistant to fewer than three classes of antibiotics] *vs* multidrug-resistant [resistant to three or four classes of antibiotics] *vs* extensively drug-resistant [resistant to five or six classes of antibiotics] and *vs* pandrug-resistant [resistant to at least seven classes of antibiotics]. Drug-resistance designation was determined at a central laboratory based on minimum inhibitory concentration.

| | Amikacin Inhale group (n=255) | Placebo group (n=253) |
|---|---|---|
| **Sex** | | |
| Male | 182 (71%) | 178 (70%) |
| Female | 73 (29%) | 75 (30%) |
| **Race*** | | |
| White | 120 (47%) | 105 (42%) |
| Asian | 103 (40%) | 108 (43%) |
| Black | 8 (3%) | 14 (6%) |
| Other | 26 (10%) | 34 (13%) |
| **Age, years** | | |
| Mean (SD) | 64·2 (16·1) | 63·9 (17·5) |
| Median (IQR) | 66·0 (56·0–76·0) | 66·0 (54·0–78·0) |
| **Age group, years** | | |
| 18–44 | 31 (12%) | 41 (16%) |
| 45–64 | 86 (34%) | 69 (27%) |
| 65–74 | 66 (26%) | 61 (24%) |
| ≥75 | 72 (28%) | 82 (32%) |
| **Geographic region** | | |
| Asia–Pacific | 103 (40%) | 107 (42%) |
| Europe | 79 (31%) | 74 (29%) |
| North America | 42 (16%) | 42 (17%) |
| Latin America | 31 (12%) | 30 (12%) |
| **APACHE II score** | | |
| Mean (SD) | 20·2 (6·2) | 20·3 (6·6) |
| Median (IQR) | 19·0 (16·0–24·0) | 20·0 (15·0–24·0) |
| **APACHE II score group** | | |
| <20 | 137 (54%) | 125 (49%) |
| ≥20 | 118 (46%) | 128 (51%) |
| **Clinical Pulmonary Infection Score†** | | |
| Mean (SD) | 7·1 (1·4) | 7·0 (1·3) |
| Median (IQR) | 7·0 (6·0–8·0) | 7·0 (6·0–8·0) |
| **Type of pneumonia** | | |
| Hospital-acquired | 73 (29%) | 74 (29%) |
| Health care-associated | 13 (5%) | 21 (8%) |
| Ventilator-associated | 125 (49%) | 116 (46%) |
| Community-acquired | 41 (16%) | 40 (16%) |
| Data missing | 3 (1%) | 2 (1%) |
| **Type of tracheal device** | | |
| Endotracheal tube | 197 (77%) | 191 (75%) |
| Tracheostomy | 44 (17%) | 52 (21%) |
| Data missing | 14 (5%) | 10 (4%) |
| **Drug-resistance designation of pathogens** | | |
| Not multidrug-resistant | 126 (49%) | 112 (44%) |
| Multidrug-resistant | 44 (17%) | 61 (24%) |
| Extensively drug-resistant | 81 (32%) | 77 (30%) |
| Pandrug-resistant | 3 (1%) | 2 (1%) |
| Data missing | 1 (<1%) | 1 (<1%) |
| **Most common pathogens (≥10% of patients)** | | |
| *Pseudomonas aeruginosa* | 75 (29%) | 88 (35%) |
| *Acinetobacter baumannii* | 77 (30%) | 69 (27%) |
| *Klebsiella pneumoniae* | 53 (21%) | 44 (17%) |
| *Escherichia coli* | 28 (11%) | 29 (11%) |
| Other | 22 (9%) | 23 (9%) |
| **Monomicrobial or polymicrobial infection** | | |
| Monomicrobial | 172 (67%) | 165 (65%) |
| Polymicrobial | 82 (32%) | 87 (34%) |
| Data missing | 1 (<1%) | 1 (<1%) |
| **Gram-stain status of infection** | | |
| Gram-negative only | 230 (90%) | 230 (91%) |
| Gram-negative and Gram-positive | 24 (9%) | 22 (9%) |
| Data missing | 1 (<1%) | 1 (<1%) |

Data are n (%) unless otherwise indicated. Study drugs were administered as an adjunct to standard-of-care intravenous antibiotics. APACHE=Acute Physiology and Chronic Health Evaluation. *Patients could self-report more than one race; Asia–Pacific was considered to comprise China, Japan, Philippines, South Korea, Taiwan, and Thailand, and Latin America was considered to comprise Brazil, Colombia, and Mexico. †Determined at study visit 1, so a few patients scored less than 6 despite having scored 6 or more at screening.

***Table 1:*** **Baseline characteristics of efficacy population**

## Statistical analysis

With agreement from the FDA, data from INHALE 1 and 2 were combined under a protocol amendment. Safety analyses were summarised descriptively in the safety population, which included all patients who received at least one dose of study drug. Efficacy analyses included all patients in the safety population who were microbiologically confirmed to be infected with at least one Gram-negative pathogen and who had an APACHE II score of at least 10 at diagnosis (efficacy population).

We estimated that a sample size of 254 patients per treatment group would achieve 81% power to detect a between-group survival difference of 11%. Percentage survival was estimated to be 80% in the Amikacin Inhale group and 69% in the placebo group. The test statistic used was a two-sided $\chi^2$ test with a significance level of 0·05. The sample size calculation was based on simulation because there is no historical reference for improved survival with Amikacin Inhale. The recruitment target for the primary efficacy analysis was increased to 724 patients (362 in each group) under the assumption that approximately 30% of patients would be ineligible for the analysis, most frequently owing to the absence of a Gram-negative pathogen and based on current surveillance. The primary efficacy analysis was tested with a Cochran–Mantel–Haenszel test of general association, adjusting for stratum and geographic region. Success in the primary endpoint was defined as a greater proportion of patients surviving at LFU visit with Amikicin Inhale than with placebo and p<0·05. Odds ratios (ORs) and 95% CIs were calculated as a supportive analysis, and Kaplan-Meier curves were generated post hoc for time to investigator assessment of unsuccessful treatment, defined as the time from the first day of study drug intake to the first timepoint

| | Amikacin Inhale group | Placebo group |
|---|---|---|
| **Primary endpoint*** | | |
| Survival at days 28–32 (n=255 *vs* n=253) | | |
| Treatment successful | 191 (75%) | 196 (77%) |
| Treatment unsuccessful | 64 (25%) | 57 (23%) |
| **Secondary endpoints** | | |
| Mortalities (n=255 *vs* n=253) | 64 (25%) | 57 (23%) |
| Pneumonia-related deaths | 43 (67%) | 36 (63%) |
| Pneumonia-unrelated deaths | 21 (33%) | 21 (37%) |
| Early clinical response (n=255 *vs* n=253)† | | |
| Achieved early response | 149 (58%) | 145 (57%) |
| Did not achieve early response | 106 (42%) | 108 (43%) |
| Duration of mechanical ventilation, days (n=255 *vs* n=252) | | |
| Mean (SD) | 20·6 (10·1) | 20·2 (10·2) |
| Median (IQR) | 28·0 (9·0–28·0) | 28·0 (8·5–28·0) |
| Duration of intensive care unit stay, days (n=247 *vs* n=249) | | |
| Mean (SD) | 21·3 (8·2) | 21·9 (8·0) |
| Median (IQR) | 28·0 (13·0–28·0) | 28·0 (14·0–28·0) |

Data are n (%), unless otherwise indicated. *p=0·43 for the difference between the Amikacin Inhale and placebo groups in treatment success; p values for secondary endpoints are not reported because the primary endpoint was not met. †Composite endpoint based on Clinical Pulmonary Infection Score on days 3, 5, and 10 (*vs* baseline); the presence of empyema or lung abscesses at days 3, 5, or 10; and all-cause mortality up to the end of therapy; early clinical response was attained if success criteria for all three CPIS determinations were met (appendix p 7), and if patients had not died or developed empyema or lung abscesses.

***Table 2:*** **Primary and secondary outcomes in the efficacy population**

at which treatment success was assessed. Patients who were successfully treated were censored at death, at their LFU visit, or at their last study visit.

Statistical software SAS (version 9.1) was used for all analyses, and the study was overseen by a data monitoring committee.

### Role of the funding source

The funder of the study provided all study drugs and complete inhalation systems, funded all analyses, and participated in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Between April 13, 2013, and April 7, 2017, 807 patients were assessed for eligibility, of whom 725 were enrolled and randomly assigned to the Amikacin Inhale group (362 patients) or the placebo group (363 patients; figure 1). Thirteen patients never received study drug for diverse medical and administrative reasons and the safety population included 354 patients in the Amikacin Inhale group and 358 patients in the placebo group. Of the safety population, 99 patients in the Amikacin Inhale group and 105 in the placebo group were excluded from the efficacy analyses because they had no culture-confirmed Gram-negative bacteria or an APACHE II score of less than 10 at pneumonia diagnosis (figure 1). 255 patients in the Amikacin Inhale group and 253 in the placebo group were therefore included in the efficacy analyses. At the EOT visit, data were still being collected for 228 patients in the Amikacin Inhale group and 224 patients in the placebo group.

Patient demographic and disease characteristics were similar at baseline in the two treatment groups (table 1). 241 (47%) of 508 patients included in the primary efficacy analysis had ventilator-associated pneumonia and 147 (29%) had hospital-acquired pneumonia (patient demographic and disease characteristics in the safety population are in the appendix p 14). Participants were treated with study drug for a median of 10 days (IQR 9–11) in both groups, and the median doses of study drug received by all participants was 20 (15–20). Collectively, *P aeruginosa* (in 163 [32%] participants), *Acinetobacter baumannii* (in 146 [29%] participants), *Klebsiella pneumoniae* (in 97 [19%] participants), and *Escherichia coli* (in 57 [11%] participants) constituted more than 90% of respiratory pathogens in this population at baseline. Approximately one-third of participants had polymicrobial infections, and less than 10% of participants were co-infected with Gram-negative and Gram-positive organisms.

191 (75%) of 255 patients in the Amikacin Inhale group and 196 (77%) of 253 patients in the placebo group survived until LFU visit. The median duration of intravenous standard-of-care antibiotics among these patients was 18 days (13–28) in the Amikacin Inhale group and 18 days (11–30) in the placebo group. At LFU visit, 64 (25%) patients in the Amikacin Inhale group and 57 (23%) patients in the placebo group had died, 96 (38%) on Amikacin Inhale and 97 (38%) on placebo were no longer being ventilated (ten [4%] *vs* 11 [4%] were in the ICU, 27 [11%] *vs* 26 [10%] were in hospital but not in the ICU, and 59 [23%] *vs* 60 [24%] had been discharged from hospital), and 95 (37%) in the Amikacin Inhale group and 99 (39%) in the placebo group were still being ventilated (40 [16%] *vs* 46 [18%] were in the ICU, 27 [11%] vs 28 [11%] were in hospital but not in the ICU, and 28 [11%] *vs* 25 [10%] had been discharged).

The primary endpoint was not met (table 2). We found no between-group difference in survival at LFU visit in the efficacy population: 191 (75%) of 255 patients in the Amikacin Inhale group versus 196 (77%) of 253 patients in the placebo group survived until LFU visit (OR 0·841, 95% CI 0·554–1·277; p=0·43). In a prespecified supporting analysis of the primary endpoint in the safety population, we found that 272 (77%) of 354 patients in the Amikacin Inhale group versus 276 (77%) of 358 patients in the placebo group survived until LFU visit (OR 0·989, 95% CI 0·694–1·408; p=0·95).

Secondary endpoints were not formally tested for significance because the primary endpoint was not met, but they did not appear to differ between the treatment groups (table 2). Around two-thirds of deaths during the study were pneumonia-related. Among the 214 patients who did not achieve an early clinical response, lack of

decline in CPIS score was the most common reason (in 81 [96%] patients in the Amikacin Inhale group *vs* 76 [70%] patients in the placebo group). Patients spent a median of 28 days in the ICU and on mechanical ventilation. No significant between-group differences were seen in analyses of other exploratory endpoints (data not shown).

In the safety population, similar proportions of patients in the two treatment groups had a TEAE or a serious TEAE (table 3). Of 11195 doses administered, 269 (2%) device events were reported (in 140 [40%] of 353 patients in the Amikacin Inhale group *vs* 129 [36%] of 359 patients in the placebo group), and 14 (<1%) device events were associated with TEAEs or serious TEAEs. Most reported device events were technical complaints with no safety implications. Events occurring in six patients in which aerosolisation might have occluded components of the ventilator circuit were investigated and attributed to procedural errors made in late changing of circuit filters. There were four serious device-related TEAEs (table 3), two potentially related to ventilator-circuit occlusion (one case of asphyxia and one case of respiratory distress), and two that were not (one case of respiratory distress and cardiac arrest, and one separate case of cardiac arrest).

Frequencies of TEAEs of special interest were similar in the two treatment groups, except bronchospasm, which occurred slightly more frequently in the Amikacin Inhale group than in the placebo group (table 3). An expanded list of TEAEs is shown in the appendix (pp 15–16). Serious TEAEs that occurred in more than one patient and only in the Amikacin Inhale group were pneumothorax (n=5), acute myocardial infarction (n=3), disseminated intravascular coagulation, acute left ventricular failure, arrhythmia, myocardial infarction, failure to thrive, renal failure, asphyxia, and bronchospasm (n=2 each). Nine serious TEAEs were considered to be related to study drug (seven in the Amikacin Inhale group and two in the placebo group); these serious TEAEs were renal failure (n=2), bronchospasm (n=2) and single instances of respiratory distress, asphyxia, and bronchial hyperreactivity in the Amikacin Inhale group, and two cases of acute kidney injury in the placebo group.

A post-hoc Kaplan–Meier plot of cumulative all-cause mortality showed that deaths in the two groups occurred at similar rates, differing by no more than 3% between baseline and LFU visit (figure 2). In post-hoc subgroup analyses, we found no effect of duration of intravenous standard-of-care antibiotic therapy on survival: 145 (79%) of 183 patients in the Amikacin Inhale group and 140 (86%) of 163 patients in the placebo group who stopped intravenous standard-of-care antibiotic therapy after the EOT visit survived compared with 45 (63%) of 71 patients in the Amikacin Inhale group and 55 (62%) of 89 patients in the placebo group who stopped this treatment at or before the EOT visit (data were missing for one patient in each group). Survival did not differ between groups by duration of intravenous antibiotic treatment before initiation of study drug, occurrence of septic shock, or geographical region (appendix p 10).

We found no between-group differences in the proportion of infections, by pathogen, that were eradicated

| | Amikacin Inhale group (n=353) | Placebo group (n=359) | Total (n=712) |
|---|---|---|---|
| **Summary** | | | |
| Any TEAE | 295 (84%) | 303 (84%) | 598 (84%) |
| Device-related | 7 (2%) | 3 (1%) | 10 (1%) |
| Study drug-related | 34 (10%) | 22 (6%) | 56 (8%) |
| Discontinuation of study drug | 31 (9%) | 24 (7%) | 55 (8%) |
| Maximum severity of any TEAE | | | |
| Mild | 80 (23%) | 96 (27%) | 176 (25%) |
| Moderate | 95 (27%) | 106 (30%) | 201 (28%) |
| Severe | 120 (34%) | 101 (28%) | 221 (31%) |
| Any serious TEAE | 101 (29%) | 97 (27%) | 198 (28%) |
| Device-related | 4 (1%) | 0 | 4 (1%) |
| Study drug-related | 7 (2%) | 2 (1%) | 9 (1%) |
| Discontinuation of study drug | 15 (4%) | 11 (3%) | 26 (4%) |
| Maximum severity of any serious TEAE | | | |
| Mild | 4 (1%) | 2 (1%) | 6 (1%) |
| Moderate | 8 (2%) | 14 (4%) | 22 (3%) |
| Severe | 89 (25%) | 81 (23%) | 170 (24%) |
| **Common TEAEs by system organ class and preferred term*** | | | |
| Blood and lymphatic system | 50 (14%) | 72 (20%) | 122 (17%) |
| Anaemia | 36 (10%) | 44 (12%) | 80 (11%) |
| Gastrointestinal disorders | 104 (29%) | 115 (32%) | 219 (31%) |
| Constipation | 30 (8%) | 32 (9%) | 62 (9%) |
| Diarrhoea | 27 (8%) | 33 (9%) | 60 (8%) |
| General and administration site conditions | 52 (15%) | 66 (18%) | 118 (17%) |
| Pyrexia | 19 (5%) | 21 (6%) | 40 (6%) |
| Infections and infestations† | 103 (29%) | 101 (28%) | 204 (29%) |
| Septic shock | 15 (4%) | 18 (5%) | 33 (5%) |
| Metabolism and nutrition | 107 (30%) | 108 (30%) | 215 (30%) |
| Hypokalaemia | 32 (9%) | 37 (10%) | 69 (10%) |
| Respiratory, thoracic, and mediastinal disorders | 83 (24%) | 89 (25%) | 172 (24%) |
| Vascular | 56 (16%) | 39 (11%) | 95 (13%) |
| Hypotension | 23 (7%) | 13 (4%) | 36 (5%) |
| **TEAEs of special interest** | | | |
| Local-effect adverse events, excluding bronchospasm | 31 (9%) | 26 (7%) | 57 (8%) |
| Bronchospasm | 15 (4%) | 4 (1%) | 19 (3%) |
| Device-related adverse event | 7 (2%) | 3 (1%) | 10 (1%) |
| Hypersensitivity | 21 (6%) | 19 (5%) | 40 (6%) |
| Nephrotoxicity | 39 (11%) | 44 (12%) | 83 (12%) |
| Ototoxicity | 0 | 1 (<1%) | 1 (<1%) |
| Neuromuscular blockade | 4 (1%) | 6 (2%) | 10 (1%) |

Data are in all patients who received at least one dose of study drug. We did not statistically test for between-group differences. One patient assigned to Amikacin Inhale received placebo in error; this patient was included in the placebo group for safety analyses but was counted among those randomly assigned to Amikacin Inhale for patient disposition. TEAE=treatment-emergent adverse event. *Events occurring in at least 20% of patients by system organ class or in at least 5% by preferred term. †Those unrelated to the patient's pneumonia.

***Table 3:*** **TEAEs in the safety population**

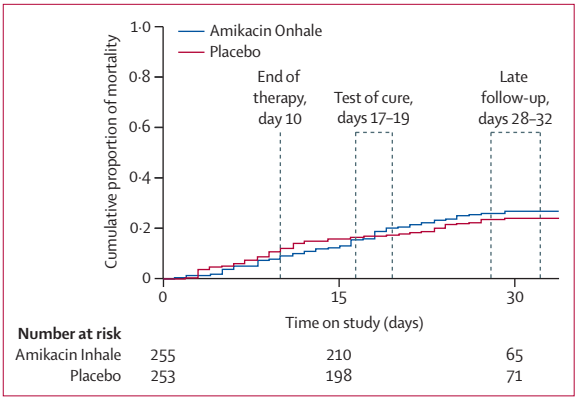


*Figure 2:* Cumulative all-cause mortality over time

at the test-of-cure visit (table 4; appendix p 9). *P aeruginosa* was eradicated most frequently (99 [61%] of 163 infections), and a post-hoc analysis showed that eradication of this pathogen occurred in a greater proportion of patients receiving Amikacin Inhale than placebo (73% *vs* 50%; p=0·0027). However, this increased eradication frequency was not associated with increased survival in patients infected with *P aeruginosa* receiving Amikacin Inhale (56 [75%] of 75 patients *vs* placebo (66 [75%] of 88 patients in the placebo group; survival data are not shown for pathogens).

We observed no between-group differences in survival based on the drug-resistance designation of the infecting pathogen (table 4). The proportions of patients surviving infection with a pathogen that was not multidrug-resistant were similar to the proportions surviving a multidrug-resistant or extensively drug-resistant infection (table 4). Among patients with treatment-emergent respiratory pathogens, nine (4%) in each group were infected with *A baumannii*, and one (<1%) patient in the Amikacin Inhale group and 11 (4%) patients in the placebo group were infected with *P aeruginosa*. Other treatment-emergent pathogens are summarised in the appendix (p 17).

| | Amikacin Inhale group | Placebo group |
|---|---|---|
| **Microbiological response** | | |
| *Pseudomonas aeruginosa* | | |
| Eradication | 55/75 (73%) | 44/88 (50%) |
| Persistence | 20/75 (27%) | 44/88 (50%) |
| *Acinetobacter baumannii* | | |
| Eradication | 46/77 (60%) | 43/69 (62%) |
| Persistence | 31/77 (40%) | 26/69 (38%) |
| *Klebsiella pneumoniae* | | |
| Eradication | 38/53 (72%) | 28/44 (64%) |
| Persistence | 15/53 (28%) | 16/44 (36%) |
| *Escherichia coli* | | |
| Eradication | 21/28 (75%) | 19/29 (66%) |
| Persistence | 7/28 (25%) | 10/29 (34%) |
| *Serratia marcescens* | | |
| Eradication | 12/16 (75%) | 13/17 (76%) |
| Persistence | 4/16 (25%) | 4/17 (24%) |
| *Enterobacter cloacae* | | |
| Eradication | 9/15 (60%) | 10/16 (63%) |
| Persistence | 6/15 (40%) | 6/16 (38%) |
| *Staphylococcus aureus* | | |
| Eradication | 12/16 (75%) | 10/15 (67%) |
| Persistence | 4/16 (25%) | 5/15 (33%) |
| *Haemophilus influenzae* | | |
| Eradication | 8/10 (80%) | 10/10 (100%) |
| Persistence | 2/10 (20%) | 0/10 |
| **Clinical response** | | |
| Not multidrug-resistant* | | |
| Survived | 98/126 (78%) | 88/112 (79%) |
| Died | 28/126 (22%) | 24/112 (21%) |
| Multidrug-resistant† | | |
| Survived | 34/44 (77%) | 48/61 (79%) |
| Died | 10/44 (23%) | 13/61 (21%) |
| Extensively drug-resistant‡ | | |
| Survived | 56/81 (69%) | 58/77 (75%) |
| Died | 25/81 (31%) | 19/77 (25%) |
| Pandrug-resistant§ | | |
| Survived | 3/3 (100%) | 2/2 (100%) |
| Died | 0/3 | 0/2 |

Data are n/N (%). Patients with a microbiological response could be counted more than once. Data on clinical response were missing from one participant from the Amikacin Inhale group and one participant from the placebo group. Rate differences (placebo minus Amikacin Inhale) were *0·8 (95% CI −9·7 to 11·3), †1·4 (−14·7 to 17·5), and ‡6·2 (−7·7 to 20·1), with all other rate differences not assessed. §Between-group difference in survival in patients infected with pandrug-resistant pathogens could not be estimated because of the small number of individuals affected.

***Table 4:*** **Microbiological response at test-of-cure visit (days 17–19) for selected baseline respiratory pathogens and clinical response by drug resistance designation**

## Discussion

In our large phase 3 trial in intubated, mechanically ventilated patients with Gram-negative pneumonia in the ICU, we found no overall survival benefit of adding inhaled amikacin, administered via Amikacin Inhale, to standard-of-care intravenous antibiotics for initial antibiotic therapy. Moreover, we found no treatment-related benefit in pneumonia-related mortality, and there were no subgroups in which inhaled amikacin produced a decisive advantage relative to placebo. Our trial was broadly representative of ventilated patients with pneumonia in ICUs, and was internationally representative, recruiting large numbers of patients from different global regions, but the process of enrolment was slower than expected. The two INHALE studies were combined, with the agreement of the FDA, to expedite recruitment of the target population. The primary objective of the trial was stringent: both treatment groups included intravenous standard-of-care antibiotic therapy, and we required demonstration of the superiority (rather

than non-inferiority) of Amikacin Inhale over placebo. Demonstrating non-inferiority in such a trial design would have been of little merit; however, demonstrating statistical superiority is inherently difficult to achieve.

Endpoint selection is challenging in trials of hospital-acquired pneumonia and ventilator-associated pneumonia owing to the heterogeneity of patients with pneumonia in the ICU.[31] Survival at LFU visit (the primary endpoint of INHALE) is a robust indicator of clinical benefit, but this outcome was not the original primary endpoint. During the trial, and before database lock, protocol amendments were made in agreement with the FDA. These amendments changed the primary endpoint from a composite endpoint that included all-cause mortality up to test-of-cure visit; adjustments to intravenous standard-of-care antibiotic therapy before the EOT visit; restrictions on continuing intravenous standard-of-care antibiotic therapy after the EOT visit; and assessment of CPIS on days 3, 5, and 10. This decision was made because all-cause mortality was considered the most objective of these outcomes, particularly if assessed later than originally intended (LFU visit rather than test-of-cure visit), and it became apparent during the trial that intravenous standard-of-care antibiotic therapy was frequently continued beyond the 10-day period stipulated in the trial design. Extended treatment with standard-of-care intravenous antibiotics might have occurred because of understandably cautious prescribing in such a seriously ill population. Retaining the antibiotic treatment rules would have needlessly classified patients showing clinical improvement as having unsuccessful treatment. Finally, the FDA recommended removal of CPIS from the primary endpoint owing to the subjective nature of the assessment. Accordingly, CPIS became a secondary endpoint, and pneumonia-related mortality was included as a key secondary endpoint; however, we detected no benefit associated with Amikacin Inhale in either of these endpoints.

The INHALE patient population was heterogeneous, in terms of the origin of pneumonia (hospital-acquired pneumonia, ventilator-associated pneumonia, health care-associated pneumonia, and community-acquired pneumonia), the infecting pathogen, and the nature of intravenous standard-of-care therapy (including the types and number of antibiotics used and duration of antibiotic treatment). We also noted variability in the standard-of-care therapy used in different ICUs and in investigator behaviour (eg, the duration of intravenous therapy). Because we observed no between-group difference in treatment effect in any of the prespecified endpoints, we did exploratory subgroup analyses to attempt to identify factors that might have contributed to the absence of effect in the overall population. Only a small number of patients (n=19; appendix p 10) received standard-of-care intravenous antibiotic therapy for more than 48 h before study drug was initiated (for instance, owing to a delay in obtaining informed consent), and no between-group difference in survival rates was seen in this subgroup. Therefore, the absence of a treatment effect is not attributable to overtreatment before enrolment, as occurred in the 2017 IASIS trial[20] of inhaled amikacin plus fosfomycin. Failure to initiate intravenous antibiotics expeditiously when there is suspicion of pneumonia could have a substantial effect on outcomes, but at least 80% of patients initiated intravenous antibiotic treatment within 48 h (data not shown).

Most patients surviving at the EOT visit continued intravenous standard-of-care therapy despite the original protocol stipulation that this constituted unsuccessful treatment. The impact of prolonged systemic antibiotic therapy on our inability to show superiority of Amikacin Inhale compared with placebo is unknown; however, we found no between-group difference in survival related to the duration of intravenous standard-of-care treatment. A previous multicentre trial[32] of intravenous standard-of-care antibiotics alone in 401 patients found no benefit associated with their prolonged use. Additionally, current guidelines for nosocomial pneumonia recommend 7 days of therapy for almost all patients. Many patients received prolonged intravenous standard-of-care therapy and remained in the ICU until LFU visit, which could also indicate that patients in INHALE were inherently unwell. Enrolment of too many patients infected with pathogens that were not multidrug-resistant, and which were susceptible to standard-of-care intravenous antibiotics, might have masked any potential survival benefit of Amikacin Inhale. Slightly more than 50% of patients in the INHALE trials had infections caused by multidrug-resistant pathogens. Survival was unaffected by Amikacin Inhale in patients with multidrug-resistant and extensively drug-resistant infections.

Amikacin concentrations in tracheal aspirates and bronchoalveolar lavage were substantially higher than those in serum (appendix pp 10, 18), but these concentrations were variable, which was a pattern also seen in the phase 2 trial.[25,26] This variability is not unusual when measuring drug concentrations in tracheal aspirates or bronchoalveolar lavage. However, it is difficult to be certain that aerosolised drug reached the sites of infection in pneumonic lungs in a uniform manner across the population. The similarity of the proportion of infections showing eradication with Amikacin Inhale and placebo at test-of-cure visit, and the overall similarity of subgroup results for Amikacin Inhale and placebo, calls into question whether the high amikacin concentrations in tracheal aspirates and bronchoalveolar lavage accurately represented drug concentrations in the infected regions of the lung. Even in subgroups with more frequent eradication with Amikacin Inhale than with placebo (eg, patients infected with *P aeruginosa*), this more frequent eradication did not translate into improved survival.

The INHALE trial was robust, representative, and among the largest trials to date in this therapy area.

The combination of use of a synchronised inhalation system and a specially formulated antibiotic solution was a pioneering approach that was intended to standardise and guarantee high drug-delivery efficiency. That such a robust approach yielded no treatment benefit opposes routine use of inhaled antibiotics in mechanically ventilated patients with pneumonia. Our findings, and those from the IASIS trial[22] of aerosolised amikacin plus fosfomycin (which was undertaken in a similar patient population) provide no evidence to support initial inhaled antibiotics in combination with intravenous standard-of-care therapy in intubated, mechanically ventilated patients with pneumonia. Inhaled antibiotics are recommended separately as rescue therapy or for use in patients with pandrug-resistant pathogens in current pneumonia guidelines, but the associated survival benefits of these treatments have not yet been studied in large randomised controlled trials.[2] Bronchospasm and hypotension occurred at slightly higher frequencies with Amikacin Inhale than with placebo but, overall, INHALE found no notable between-group differences in the frequencies of TEAEs, and serum concentrations of amikacin were low. These observations should guide other investigators regarding endpoints and trial design that should be incorporated in future studies of aerosolised antibiotics.

#### Contributors

All authors contributed equally to the study design, data collection, data interpretation, and writing of the manuscript. JA, FB, KC, and RL additionally analysed the data.

#### Declaration of interests

MSN reports grants from Bayer and Merck for clinical research and as a paid consultant to Bayer, Merck, Paratek Pharmaceuticals, Pfizer, and Shionogi. JA was an employee of Bayer during the conduct of the study and holds Bayer stock. MB reports participation in advisory boards for or receipt of speaker honoraria (or both) from Achaogen, Angelini Pharma, Astellas Pharma, AstraZeneca, Bayer, Basilea, Cepheid, Cidara Therapeutics, Gilead Sciences, The Medicines Company, Menarini, Merck Sharp and Dohme, Nabriva, Paratek Pharmaceuticals, Pfizer, Roche, Shionogi, Tetraphase, VenatoRx Pharmaceuticals, and Vifor Pharma. FB and RL are employees of Bayer. BC reports grants from bioMérieux and Pfizer for clinical research. KC was an employee of Novartis during the conduct of the study. RD reports honoraria from AstraZeneca, Bayer, GlaxoSmithKline, and UptoDate. KSK reports consultancy fees from Achaogen, Melinta Therapeutics, Merck, Shionogi, and Zavante. PM is an employee of Covance. DPN rreports consultant fees or research funding from Achaogen, Bayer, Cepheid, Melinta Therapeutics, Merck, Pfizer, Shionogi, and Tetraphase. GCW reports honoraria or research funding from Bayer, Cubist Pharmaceuticals, and Theravance Biopharma. RGW reports participation in a clinical evaluation committee for a Pfizer-sponsored antibiotic trial and consultancy fees from Achaogen, Arsanis, Bayer, The Medicines Company, Merck, Pfizer, Polyphor, and Shionogi. JC reports personal fees from Accelerate Diagnostics, from AstraZeneca/Medimmune, Bayer, Brahms, Cubist/Merck, GlaxoSmithKline, Inotrem, Kenta/Aridis, Pfizer, Shionogi, and Tigenix, outside the submitted work. CW declares no competing interests.

#### Data sharing

Individual participant data (including data dictionaries) and analyses will not be shared. The study protocol and statistical analysis plan for the INHALE trial are available in the appendix, and the trial information is available online.

For the **trial information** see https://clinicaltrials.gov/ct2/show/study/NCT01799993?term=Amikacin+INhale&rank=1&sect=X80156

#### Acknowledgments

The INHALE clinical trial programme was funded by Bayer, and Highfield Communication provided medical writing and editorial assistance for the development of this manuscript.

#### References

1 Torres A, Niederman MS, Chastre J, et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT). *Eur Respir J* 2017; **50:** 1700582.

2 Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis* 2016; **63:** e61–111.

3 Mehta AB, Syeda SN, Wiener RS, Walkey AJ. Epidemiological trends in invasive mechanical ventilation in the United States: a population-based study. *J Crit Care* 2015; **30:** 1217–21.

4 American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005; **171:** 388–416.

5 Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; **44** (suppl 2)**:** S27–72.

6 Chastre J, Wunderink R, Prokocimer P, Lee M, Kaniga K, Friedland I. Efficacy and safety of intravenous infusion of doripenem versus imipenem in ventilator-associated pneumonia: a multicenter, randomized study. *Crit Care Med* 2008; **36:** 1089–96.

7 Kollef MH, Chastre J, Clavel M, et al. A randomized trial of 7-day doripenem versus 10-day imipenem–cilastatin for ventilator-associated pneumonia. *Crit Care* 2012; **16:** R218.

8 Awad SS, Rodriguez AH, Chuang YC, et al. A phase 3 randomized double-blind comparison of ceftobiprole medocaril versus ceftazidime plus linezolid for the treatment of hospital-acquired pneumonia. *Clin Infect Dis* 2014; **59:** 51–61.

9 Brun-Buisson C, Sollet JP, Schweich H, Brière S, Petit C. Treatment of ventilator-associated pneumonia with piperacillin–tazobactam/amikacin versus ceftazidime/amikacin: a multicenter, randomized controlled trial. *Clin Infect Dis* 1998; **26:** 346–54.

10 Udy AA, Roberts JA, Lipman J. How should we dose antibiotics for pneumonia in the ICU? *Curr Opin Infect Dis* 2013; **26:** 189–95.

11 Roberts JA, Abdul-Aziz MH, Lipman J, et al. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. *Lancet Infect Dis* 2014; **14:** 498–509.

12 Nicolau DP, Dimopoulos G, Welte T, Luyt CE. Can we improve clinical outcomes in patients with pneumonia treated with antibiotics in the intensive care unit? *Expert Rev Respir Med* 2016; **10:** 907–18.

13 Schliamser SE, Cars O, Norrby SR. Neurotoxicity of beta-lactam antibiotics: predisposing factors and pathogenesis. *J Antimicrob Chemother* 1991; **27:** 405–25.

14 Avent ML, Rogers BA, Cheng AC, Paterson DL. Current use of aminoglycosides: indications, pharmacokinetics and monitoring for toxicity. *Intern Med J* 2011; **41:** 441–49.

15 Lodise TP, Sorgel F, Melnick D, Mason B, Kinzig M, Drusano GL. Penetration of meropenem into epithelial lining fluid of patients with ventilator-associated pneumonia. *Antimicrob Agents Chemother* 2011; **55:** 1606–10.

16 Bassetti M, Luyt CE, Nicolau DP, Pugin J. Characteristics of an ideal nebulized antibiotic for the treatment of pneumonia in the intubated patient. *Ann Intensive Care* 2016; **6:** 35.

17 Palmer LB. Aerosolized antibiotics in the intensive care unit. *Clin Chest Med* 2011; **32:** 559–74.

18 Zampieri FG, Nassar AP Jr, Gusmao-Flores D, Taniguchi LU, Torres A, Ranzani OT. Nebulized antibiotics for ventilator-associated pneumonia: a systematic review and meta-analysis. *Crit Care* 2015; **19:** 150.

19 Russell CJ, Shiroishi MS, Siantz E, Wu BW, Patino CM. The use of inhaled antibiotic therapy in the treatment of ventilator-associated pneumonia and tracheobronchitis: a systematic review. *BMC Pulm Med* 2016; **16:** 40.

20 Kollef MH, Ricard JD, Roux D, et al. A randomized trial of the amikacin fosfomycin inhalation system for the adjunctive therapy of Gram-negative ventilator-associated pneumonia: IASIS trial. *Chest* 2017; **151:** 1239–46.

21 Wood GC. Aerosolized antibiotics for treating hospital-acquired and ventilator-associated pneumonia. *Expert Rev Anti Infect Ther* 2011; **9:** 993–1000.

22 Solé-Lleonart C, Rouby JJ, Blot S, et al. Nebulization of antiinfective agents in invasively mechanically ventilated adults: a systematic review and meta-analysis. *Anesthesiology* 2017; **126:** 890–908.

23 Dhand R. The role of aerosolized antimicrobials in the treatment of ventilator-associated pneumonia. *Respir Care* 2007; **52:** 866–84.

24 Le J, Ashley ED, Neuhauser MM, et al. Consensus summary of aerosolized antimicrobial agents: application of guideline criteria. *Pharmacotherapy* 2010; **30:** 562–84.

25 Ehrmann S, Chastre J, Diot P, Lu Q. Nebulized antibiotics in mechanically ventilated patients: a challenge for translational research from technology to clinical care. *Ann Intensive Care* 2017; **7:** 78.

26 Luyt CE, Clavel M, Guntupalli K, et al. Pharmacokinetics and lung delivery of PDDS-aerosolized amikacin (NKTR-061) in intubated and mechanically ventilated patients with nosocomial pneumonia. *Crit Care* 2009; **13:** R200.

27 Niederman MS, Chastre J, Corkery K, Fink JB, Luyt CE, García MS. BAY41-6551 achieves bactericidal tracheal aspirate amikacin concentrations in mechanically ventilated patients with Gram-negative pneumonia. *Intensive Care Med* 2012; **38:** 263–71.

28 Dhand R, Sohal H. Pulmonary drug delivery system for inhalation therapy in mechanically ventilated patients. *Expert Rev Med Devices* 2008; **5:** 9–18.

29 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH harmonised tripartite guideline: guideline for good clinical practice E6 (R1). June 10, 1996. https://apps.who.int/medicinedocs/documents/s22154en/s22154en.pdf (accessed March 21, 2019).

30 World Medical Association. WMA Declaration of Helsinki—ethical principles for medical research involving human subjects. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ (accessed March 21, 2019).

31 Niederman MS. Hospital-acquired pneumonia, health care-associated pneumonia, ventilator-associated pneumonia, and ventilator-associated tracheobronchitis: definitions and challenges in trial design. *Clin Infect Dis* 2010; **51** (suppl 1)**:** S12–17.

32 Chastre J, Wolff M, Fagon JY, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA* 2003; **290:** 2588–98.