

Official Title:	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
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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

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- Amendment Number 1.0
Forming integrated protocol Version 2.0, Dated 17 AUG 2009
- Amendment Number 2.0
Forming integrated protocol Version 1.0, Dated 14 JUN 2010
- Amendment Number 3.0
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- Amendment Number 4.0
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- Amendment Number 5.0
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- Amendment Number 6.0
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- Amendment Number 8.0
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Modifications are summarized in Section [16.8](#)

This document integrates the original protocol and all global amendments.



1. Title Page - amended

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

Test Drug: BAY 41-6551 (Amikacin Solution for Inhalation and the Pulmonary Drug Delivery System [PDDS Clinical])

Clinical study phase: III **Date:** 29 Aug 2017

EudraCT no.:¹ 2013-001048-73 **Version no.:** 9.0

Study Number: 13084

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The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

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¹ Per Amendment 5

² Per Amendment 5



Signature of the sponsor's medically responsible persons ³

The signatories agree to the content of the final clinical study protocol as presented.

Name: PPD [redacted]

Role: PPD [redacted]

Signature: PPD [redacted]

ate:

Oct 16, 2017

³ Changed per Amendments 5, 6 and 8



Signature of the principal investigator

The signatory agrees to the content of the final clinical study protocol as presented.

Name:

Affiliation:

Date:

Signature:

Signed copies of this signature page are stored in the sponsor's study file and in the respective center's investigator site file.

2. Synopsis - amended

Title	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
Study phase	III
Investigational product, dosage, and route of administration	BAY 41-6551 (Amikacin Solution for Inhalation and the Pulmonary Drug Delivery System [PDDS Clinical])
Reference product	Standard of care antimicrobial treatment with consideration to include two antibiotics as per the 2005 American Thoracic Society (ATS) / Infectious Diseases Society of America (IDSA) Guidelines for the Management of Hospital-Acquired Pneumonia (HAP), Ventilator-Associated Pneumonia (VAP), or Healthcare-Associated Pneumonia (HCAP)
Project code	214510
Indication	Gram-negative pneumonia
Diagnosis and main criteria for inclusion/exclusion⁴	<p>Patients of age 18 and older, who are hospitalized, have pneumonia suspected or confirmed to be caused by Gram-negative organisms, and who are intubated and mechanically-ventilated will be selected for this study. In all patients where the pathogen is suspected of being Gram-negative, it should be confirmed as soon as culture results are available. Patients with microbiologically-confirmed pneumonia are those who have a Gram-negative organism cultured from an appropriate respiratory tract specimen. The main inclusion criteria are:</p> <ul style="list-style-type: none"> • Males and non-pregnant, non-lactating females, 18 years of age or older • Intubated and mechanically-ventilated • Diagnosis of pneumonia defined as presence of a new or progressive infiltrate(s) on chest radiograph • Presence of Gram-negative organism(s) indicated by Gram-stain, or culture of pre-therapy respiratory specimen, or suspected Gram-negative pathogen • Impaired oxygenation • Clinical Pulmonary Infection Score (CPIS) \geq 6 • The presence of a MDR organism in a pre-therapy respiratory specimen OR at least two risk factors for MDR organisms
	<p>The main exclusion criteria are:</p> <ul style="list-style-type: none"> • A history of hypersensitivity to amikacin or other aminoglycosides • Has received antibiotic therapy for Gram-negative pneumonia for greater than 48 hours at the time of randomization • Has primary lung cancer (including patients with small cell

⁴ Per Amendment 5 and 8

	<p>lung carcinoma/non-small cell lung carcinoma and patients with unknown histology) or another malignancy metastatic to the lungs or other known endobronchial obstructions.</p> <p>Exception: Please note that patients with complete resection of non-small cell lung carcinoma are eligible for the study.</p> <ul style="list-style-type: none">• Known or suspected active tuberculosis, cystic fibrosis, human immunodeficiency virus (HIV) infection with CD 4 count < 200 cell/mm³, or invasive fungal infection of the lung, lung abscess, or empyema• Known or suspected bacteremia secondary to <i>Staphylococcus aureus</i>• Known or suspected neuromuscular disorders such as myasthenia gravis or parkinsonism• Has had a stroke within five days• A positive urine and/or serum beta-human chorionic gonadotropin (β-hCG) pregnancy test• Burns greater than 40% of total body surface area• Patients with a serum creatinine > 2 mg/dL (177 μmol/L) <p>Exception: Patients with a serum creatinine > 2 mg/dL (177 μmol/L) and being treated with continuous renal replacement therapy (continuous veno-venous hemofiltration [CVVH] and continuous veno-venous hemofiltration with dialysis[CVVH-D]) or daily hemodialysis will receive the aerosol study drug treatment (Section 8.4.6.1)</p> <ul style="list-style-type: none">• Neutropenia (screening absolute neutrophil count [ANC] < 10³ neutrophils/mm³)• Has been on mechanical ventilation for > 28 days• Is participating in or has participated in other investigational interventional studies within the last 28 days prior to study treatment• The risk of rapidly fatal illness and death within 72 hours, or any concomitant conditions not related to VAP that, in the opinion of the investigator, precludes completion of study evaluations and the course of therapy• Stem cell transplantation• Patients with documented Legionella infection (eg, Legionella pneumonia)• Has an Acute Physiology and Chronic Health Evaluation II (APACHE II) score < 10• Patients receiving veno-venous extracorporeal circulation membrane oxygenation (V-V ECMO)
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Study objectives ⁵	The study objective is to demonstrate that as adjunctive therapy to (intravenous) 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. The primary efficacy variable is Survival as defined in Section 8.2. The secondary objectives are to evaluate the superiority of aerosolized BAY 41-6551 versus aerosolized placebo in pneumonia-related mortality, the Early Clinical Response at Day 10, the days on ventilation, and the days in the ICU.
Safety endpoints ⁶	The safety endpoints are to compare (BAY 41-6551 vs aerosolized placebo, as adjunctive therapy to IV antibiotics in both arms) as measured by: <ul style="list-style-type: none"> • The frequency of adverse events (AEs) • The progression and incidence rates of organ failure • The all-cause mortality rate during therapy, at Day 15 and at Day 28 (also the primary efficacy endpoint)
Patient population ⁷	Randomized, adult patients (age ≥18 years) with a microbiologically-confirmed pneumonia caused by Gram-negative organisms who received at least one dose of study drug and have an APACHE II score ≥ 10 at the time of diagnosis of pneumonia (modified Intent-to-Treat [mITT] population) will be analyzed in the primary efficacy analysis.
Study design ⁸	This is a prospective, randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety and efficacy of 10 calendar day (20 doses) course of aerosolized BAY 41-6551 400 mg (amikacin as free base) every 12 hours versus aerosolized placebo (normal saline), as adjunctive therapy to IV antibiotics in both arms, in intubated and mechanically-ventilated patients with known or suspected Gram-negative pneumonia. All patients will receive parenteral antibiotics with consideration to include 2 antibiotics as per the 2005 ATS/IDSA guidelines for 10 days. Patients who are extubated before completing the full course (10 calendar days if the first dose is administered in the AM or 11 calendar days if the first dose is administered in the PM [20 doses]) of aerosol therapy will be continued on aerosolized therapy with the handheld adaptor. (Section 8.2)
Concurrent control ⁹	Aerosolized placebo
Duration of treatment	10 full days

⁵ Per Amendment 6 and 8

⁶ Per Amendment 6 and 8

⁷ Per Amendment 6

⁸ Per Amendment 6

⁹ Per Amendment 6

<p>Methodology ¹⁰</p>	<p>Eighteen to 22 days after completing 10 days of aerosolized treatment, patients will be evaluated for Survival. Patients who survive through the late follow up visit are considered a success, patients who suffer mortality for any reason on or before the Late Follow-up (LFU) visit are considered a failure.</p>
<p>Efficacy variables ¹¹</p>	<p>The primary efficacy variable will be Survival in the mITT population (ie, the ITT population who prove to be culture positive for a Gram-negative pathogen and have an APACHE II score \geq 10). Survival is achieved when the patient is documented as alive through the LFU visit.</p> <p>The secondary objectives are to evaluate the efficacy of BAY 41-6551 (versus aerosolized placebo), as adjunctive therapy to IV antibiotics in both arms, as measured by:</p> <ul style="list-style-type: none"> • Pneumonia-related mortality to the LFU visit • Early Clinical Response based on CPIS scores, the presence of empyema or lung abscess, and all-cause mortality through Day 10 • The number of days on mechanical ventilation through the LFU visit (Day 28-32) • The number of ICU days assessed at the LFU visit (Day 28-32) <p>Three additional analysis of clinical success will be conducted.</p> <ul style="list-style-type: none"> • Clinical success using the Foundation for the National Institute of Health (FNIH) recommendations is defined as mITT patients who survived through the LFU visit and did not have septic shock. • Investigator Assessment of Patient Outcome will be determined at the TOC visit (Day17-19). The investigator will assess patient signs and symptoms at the TOC visit. • Clinical Success will be evaluated using 5 component criteria, which were the former primary end point for this study.
<p>Microbiology variables ¹²</p>	<p>Secondary microbiological objectives will include comparisons (aerosolized BAY 41-6551 versus aerosolized placebo), as adjunctive therapy to IV antibiotics in both arms, of the:</p> <ul style="list-style-type: none"> • per pathogen microbiological response rates at the TOC visit • per patient microbiological response rate at the TOC visit • microbiological recurrence rates at the TOC and LFU visits • emergence of new respiratory pathogens during the aerosol treatment period, Days 1-10 • emergence of resistance among baseline pathogens in those patients with persistent infection or colonization

¹⁰ Per Amendment 6 and 8

¹¹ Per Amendment 6 and 8

¹² Per Amendment 6



<p>Safety variables</p>	<p>All patients who have received at least one dose of the study drug(s) will be evaluated for safety in a descriptive manner. The safety analysis will include tabulation of the type (using Medical Dictionary for Regulatory Activities [MedDRA] glossary) and frequency of all AEs. Drug-related AEs, serious AEs (SAEs), and premature discontinuations due to AEs will also be summarized, as well as AEs by severity, outcome, and action taken. Incidence tables will be presented for all AEs up to seven days after the end of treatment and for SAEs up to Day 28 visit. All laboratory data will be analyzed using descriptive statistics including identification of laboratory data outside normal ranges. Rates of organ failure will also be summarized by patient as well as by specific organ type. Mortality during the treatment period, and on Day 15 and Day 28 visit will be summarized.</p>
<p>Number of study centers ¹³</p>	<p>Approximately 130 study centers in North America, South America, Asia Pacific, and Europe.</p>
<p>Total number of patients ¹⁴</p>	<p>Approximately a combined total of 724 ITT patients will be recruited to this study and to study 13085 (being conducted in different countries; the protocols are identical with the exception that study 13085 has a pharmacokinetic substudy). The 724 total patients will be recruited competitively between studies 13084 and 13085; there are no minimum requirements for recruitment totals in either study. The patients will be randomized 1:1 to receive either 400 mg BAY 41-6551 (amikacin as free base) every 12 hours or aerosolized placebo every 12 hours in addition to ATS/IDSA guided IV antibiotic therapy to allow for completion of at least 472 evaluable mITT patients in the primary efficacy analysis.</p>

¹³ Per Amendment 5

¹⁴ Revised with Amendments 5 and 6

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4. Glossary and Abbreviations ¹⁵ - amended

AARC	American Association for Respiratory Care
AC/DC adaptor	alternating current/direct current adaptor
AE	Adverse event
ALT	alanine aminotransferase
ANC	Absolute neutrophil count
AP	Aeroneb Pro
APACHE II	Acute Physiology and Chronic Health Evaluation II
ARDS	Acute respiratory distress syndrome
AST	aspartate aminotransferase
ATS	American Thoracic Society
BAL	Bronchoalveolar lavage
β-hCG	beta-human chorionic gonadotropin
BMI	Body mass index
BUN	Blood urea nitrogen
CD 4	Antigenic marker on helper/inducer T cells
CFR	Code of Federal Regulations
CPIS	Clinical Pulmonary Infection Score
CRF	Case report form
CRO	Contract Research Organization
CT	Computed tomography
CVVH	Continuous veno-venous hemofiltration
CVVH-D	Continuous veno-venous hemofiltration with dialysis
CXR	Chest X-ray
DMC	Data Monitoring Committee
ECMO	Extracorporeal circulation membrane oxygenation
eCRF	Electronic case report form
EOT	End of therapy
ESBL	Extended Spectrum Beta-Lactamase
FDA	Food and Drug Administration
FNIH	Foundation for the National Institute of Health
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
H	hour(s)
HAP	Hospital-acquired pneumonia
HCAP	Healthcare-associated pneumonia
HD	Hemodialysis
HIV	Human immunodeficiency virus
HME	Heat-moisture exchanger
IB	Investigators' Brochure
ICF	Informed consent form
ICH	International Council for Harmonization
ICU	Intensive care unit
IDSA	Infectious Disease Society of America
IEC	Independent Ethics Committee
IM	Intramuscular
IME	Important medical event
IRB	Institutional Review Board
ITT	Intent-to-Treat

¹⁵ Per Amendments 5 and 6

IV	Intravenous
IVRS	Interactive voice response system
LAR	legally authorized representative
LDH	Lactate dehydrogenase
LFU	Late Follow-Up
MDR	Multidrug-resistant
MedDRA®	Medical Dictionary for Regulatory Activities
MIC	Minimum inhibitory concentration
mITT	Modified Intent-to-Treat
MN	AirLife™ Misty Neb™
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
NIH	National Institute of Health
NOAEL	no-observed-adverse-effect level
NP	Nosocomial pneumonia
PDDS	Pulmonary Drug Delivery System
PEEP	Positive end-expiratory pressure
P/F	PaO ₂ /FiO ₂
PI	Principal investigator
PO	Per os (Latin), By mouth
PSB	Protected specimen brush
Q	Quaque (Latin), Every
RBC	Red blood cell
SAE	Serious adverse event
SGOT	serum glutamic oxalo-acetic transaminase
SGPT	serum glutamate pyruvate transaminase
SMQ	Standard medical queries
SUSAR	Suspected/Unexpected Serious Adverse Reaction
TA	Tracheal aspirate
TOBI®	Tobramycin
TOC	Test-of-Cure
V-A	Veno-arterial (as in ECMO)
V-V	Veno-venous (as in ECMO)
VAP	Ventilator-associated pneumonia
WBC	White blood cell

5. Introduction

5.1 Background and Rationale - amended

Amikacin is a well-known aminoglycoside antibiotic used intravenously (IV) or intramuscularly (IM) for the treatment of infections caused by Gram-negative bacteria. Its spectrum of activity makes it suitable for use in nosocomial pneumonia patients where Gram-negative organisms are major pathogens. It has been administered and studied at several clinical centers as an aerosol treatment in patients with chronic, suppurative lung disease such as cystic fibrosis and bronchiectasis.^{1,2} Several reports describe the use of aerosolized antibiotics, such as amikacin, as adjuncts to the therapy of ventilated patients with deep lung infections, specifically ventilator-associated pneumonia (VAP)³ and tracheobronchitis.⁴ Efforts to develop such therapies and to deliver high lung doses have been hampered by the low efficiency of pulmonary drug delivery when using conventional nebulizers connected to ventilator circuits.

¹⁶Inhalation delivery of BAY 41-6551 (amikacin solution for inhalation) offers an attractive addition to IV or IM delivery. Inhalation administration minimizes systemic exposure while delivering drug directly to the site of infection. Bayer is investigating the use of aerosolized BAY 41-6551 for the treatment of serious bacterial respiratory infections in intubated and mechanically-ventilated patients using a proprietary high efficiency Pulmonary Drug Delivery System (PDDS Clinical).

The 2005 American Thoracic Society (ATS) / Infectious Diseases Society of America (IDSA) guidelines combine hospital-acquired pneumonia (HAP), VAP, and healthcare-associated pneumonia (HCAP) in the same spectrum of disease, and recommend therapy for patients with these diseases who have risk factors for multidrug-resistant (MDR) pathogens.⁵ Clinically, patients with the combination of Gram-negative pneumonia, mechanical ventilation, and risk factors for MDR pathogens present similarly, and are managed in a standard fashion regardless of whether mechanical ventilation preceded, or followed, the onset of pneumonia.

Hospital-acquired pneumonia, VAP, and HCAP are the most common nosocomial infections and represent the leading cause of death from infections that are acquired in the hospital. The incidence of nosocomial pneumonia (NP) ranges from five to ten cases per 1,000 hospital admissions in patients without major risk factors, but increases six- to twenty-fold in intensive care unit (ICU) patients who are receiving mechanical ventilation.⁶ The duration of stay in the ICU and the duration of mechanical ventilation are the major predisposing factors for acquiring NP. Ventilator-associated pneumonia is a severe respiratory infection with an associated mortality in the range of 25% to 50%^{7,8} despite broad-spectrum antibiotic therapy. Hospital-acquired pneumonia, VAP, and HCAP are major causes of morbidity and mortality despite progress in antimicrobial therapy, supportive care, and preventative measures. Ventilator-associated pneumonia complicates the hospital course of 8% to 28% of patients who require mechanical ventilation and the risk increases with increasing time on the

¹⁶ Per Amendment 8

ventilator.⁷ Gram-negative pathogens are causative organisms in approximately 60% of cases.⁷ Hospital-acquired pneumonia accounts for up to 25% of all ICU infections (90% of episodes of HAP occur during mechanical ventilation), with an associated mortality estimated to be between 33% and 50%.⁹ Additionally, the rates of HAP due to MDR organisms have increased significantly in the ICU.¹⁰

Several investigators have shown that in VAP, patients who receive appropriate antibiotics have a good clinical response within the first 6 days of treatment.^{11, 45} Prolonged therapy (14 to 21 days) leads to colonization of antibiotic-resistant bacteria, which may precede a recurrent episode of VAP. Others have shown that treatment courses as short as 3 days (versus 10 to 21 days) resulted in better clinical outcomes; however, many of these patients may not have had pneumonia.¹² Finally, a multicenter randomized controlled trial demonstrated that initial empiric therapy of VAP for 8 days had similar outcomes versus treatment for 14 days; however, a trend to greater rates of relapse for short-duration therapy was seen if the causative organism was *P.aeruginosa* or an *Acinetobacter* species.¹³ In summary, if patients receive an initially appropriate antibiotic regimen, efforts should be made to shorten the duration of therapy from the traditional 14 to 21 days to periods as short as 7 days, provided that the etiologic pathogen is not *P.aeruginosa*, and that the patient has a good clinical response with resolution of clinical features of infection.

While Gram-negative organisms can be treated with IV aminoglycoside antibiotics, parenteral delivery can cause significant adverse systemic side effects (eg, neurotoxicity, nephrotoxicity, and ototoxicity) and results in poor penetration of drug into respiratory secretions.¹⁴ Local application to the lung has been shown to have rapid kinetics and a high therapeutic index.^{3, 15, 16} Although aerosolized BAY 41-6551 has been demonstrated to offer benefit to non-intubated patients with bacterial infections, the impact in mechanically-ventilated patients has been less clear. Several investigators over the past 25 years have reported efforts to supplement IV therapy with aerosolized antibiotics, delivered via conventional nebulizers, with mixed results.⁴ There is continued interest in aerosolized antibiotics in the critical care setting, which if delivered with higher efficiency than is possible with conventional nebulizers, may prove useful as adjunctive therapy.^{17, 18}

During normal conditions of mechanical ventilation, standard pneumatic (jet) nebulizers deliver less than 10% of the nominal dose to the patient's lungs due to high residual drug volumes, loss of drug in the ventilator circuit and endotracheal tube, and loss to the atmosphere via the expiratory limb.^{17, 19} By contrast, the PDDS Clinical is designed to deliver approximately 50% of the nominal dose to the lungs, based on *in vitro* data for both the on-ventilator and handheld (off-ventilator) configurations (data on file, Novartis Report No. IDD061A_TESTR_699-ProdSpecStudy_01, May 2012).

¹⁷This clinical study will evaluate the Survival rate of patients treated with aerosolized amikacin, administered via PDDS Clinical, to that of aerosolized placebo (normal saline solution), as adjunctive therapy to IV antibiotics in both arms, in patients with microbiologically-confirmed Gram-negative pneumonia. The PDDS Clinical is expected to

¹⁷ Sentence revised with Amendment 6 and 8.

be a more efficient way of delivering aerosolized medication than a conventional pneumatic system. The study will also provide information on the safety and tolerability of aerosolized amikacin.

5.2 Risk Factors

The incidence of NP is associated with many factors, with mechanical ventilation and the duration of ventilation being primary causes of HAP, VAP, or HCAP occurrence. NP was associated with mechanical ventilation in 86% of cases in one study, and the risk for acquiring VAP increased from 5% in patients who received mechanical ventilation for 5 days to over 69% for patients who received mechanical ventilation for 30 days.^{10, 20} Other risk factors included witnessed aspiration, use of paralytic agents, and a primary admitting diagnosis of burns, trauma, or disease of the central nervous, respiratory, or cardiac systems.²¹

5.3 Bacteriology

The identification of microorganisms reported to be responsible for HAP, VAP, and HCAP varied substantially across different institutions, and was affected by factors such as underlying disease, previous antibiotic use, diagnostic methods, and local patterns of antibiotic-resistant organisms. Hospital-associated pneumonia, VAP, and HCAP may be attributed to multiple organisms. Gram-positive microorganisms isolated in patients with VAP included: *Staphylococcus aureus*, *Streptococcus pneumoniae*, and enterococci. Gram-negative microorganisms isolated in VAP patients included: *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, *Proteus* species, *Serratia* species, *Citrobacter* species, *Hafnia alvei*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia*.^{7, 22-24}

Current therapeutic management strategies for adults with HAP, VAP and HCAP are based on the 2005 ATS/IDSA guidelines.⁵

5.4 Aerosolized Antibiotic Therapy

5.4.1 Animal Studies

Accumulation of amikacin was observed in the rat lung after 14 consecutive days of nose-only inhalation exposure ranging from 20 to 109 mg/kg/day total inhaled nebulized amikacin (data on file, Bayer Report PH 36378, AT06142). Amikacin (548 µg/g ± 1.13) was detected in lung tissue, but not plasma after a 2-week treatment-free period in high dose animals. Histological findings and bronchoalveolar lavage changes were suggestive of an affected surfactant homeostasis, possibly by amikacin bound to surfactant constituents with subsequent engulfment by alveolar macrophages serving as a depot for amikacin. While no extrapulmonary toxicity was observed in this study, a no-observed-adverse-effect level (NOAEL) was not established in regard to local effects to the respiratory tract in the rat.

Recently, Goldstein²⁵ studied the administration of 45 mg/kg nebulized amikacin in piglets with experimentally induced *E. coli* pneumonia. Amikacin concentrations in lung tissue homogenates were influenced by the severity of the lung lesions. Amikacin concentration in “mild” areas of pneumonia averaged 188 ± 175 µg/g, while in “severe” areas it averaged 40 ± 65 µg/g. In all cases, lung tissue levels were lower than those previously seen by the same group in studies of healthy piglets. Nonetheless, nebulized amikacin resulted in lung tissue

concentrations much higher (up to 30 times) than those resulting from the IV infusion of 15 mg/kg amikacin. In addition, lung tissue concentrations exceeded the minimum inhibitory concentrations (MICs) of common respiratory pathogens and 71% of the lung specimens cultured were negative for bacteria versus 16% in the IV group. These investigators had also demonstrated a lack of lung tissue or systemic accumulation with four days of repeat aerosol dosing of amikacin in the same piglet model without experimentally induced *E. coli* pneumonia.²⁶ Noting that only half of the dose nominally administered to the lung was eliminated in the urine, the lack of lung tissue accumulation was attributed to removal by successive suctioning and/or physiologic mucociliary clearance.

5.4.2 Human Studies - amended

Aerosolized antibiotics have been administered to critically ill patients to treat pulmonary infections in hospitalized patients and have been investigated in clinical studies for the prevention and treatment of pneumonia in hospitalized patients.^{3,24} The advantages of inhalation therapy include delivery of high doses directly to the site of infection and low systemic exposure with the potential for reducing systemic adverse events (AEs) such as neurotoxicity, nephrotoxicity, and ototoxicity.²⁷⁻³⁰ To date, only tobramycin for inhalation (TOBI[®]) is approved in the United States for inhalational administration and labeled specifically for the management of *Pseudomonas aeruginosa* infections in patients with cystic fibrosis. TOBI[®] is not approved for the therapy of acute pulmonary exacerbations of cystic fibrosis. TOBI[®] is also approved in Europe for the treatment of cystic fibrosis.

Though their use in aerosolized form has not been approved by the Food and Drug Administration (FDA), limited clinical and scientific testing of nebulized antibiotics has been conducted to determine and evaluate the pharmacokinetics and potential effectiveness of these agents in aerosolized form. These agents, however, have not been evaluated for safety or effectiveness in randomized, controlled studies.^{3,31-34} It is anticipated that aerosol delivery of these agents to treat pulmonary infections will offer potential advantages over parenteral routes of administration, as aerosol administration delivers medication directly to the site of infection. Aerosol delivery of BAY 41-6551 may also minimize systemic exposures that, when administered by IV, are associated with AEs such as nephrotoxicity and irreversible ototoxicity.

In clinical studies, amikacin has been aerosolized in nominal doses from 400 mg to 1200 mg.^{1-2,35-40} As with other aminoglycosides, systemic absorption is low and serum levels remain far below the standard trough levels that guide IV dosing.^{2,3} Thus, the tolerance to inhalation and low systemic exposure appear to convey a high therapeutic index. The fate of the inhaled drug may be assessed by measurement of sputum drug concentrations after tracheal aspiration³ and by 24-h urine collection.^{2,36}

The longest duration of therapy reported for aerosolized amikacin was up to three weeks in ventilator-dependent patients with tracheobronchitis³ and up to two weeks in ambulatory patients with cystic fibrosis.¹ In both studies, there was reported to be a favorable impact on sputum cultures. Standridge *et al.*⁴⁰ described a patient whose resolution of community-acquired pneumonia appeared to be hastened by aerosolized amikacin.

The BAY 41-6551 and PDDS Clinical safety experience is based on the five completed studies: AMIK-02-01, AMIK-04-02, 06-IN-AK003, 06-IN-AK004, and 06-IN-AK005 (data on file, Bayer Report Number RD00002318.00).

The first study (a pilot study, AMIK-02-01) compared delivery of BAY 41-6551 via an early prototype of the PDDS Clinical versus Nektar's marketed critical care nebulizer, the Aeroneb Pro[®] (AP), and the AirLife[™] Misty Neb[™] (MN), a pneumatic nebulizer, in mechanically-ventilated patients. Twelve patients on volume-cycled ventilation were enrolled to receive 125 mg/mL sulfite-free BAY 41-6551 on separate study days (≥ 2 days washout) in randomized order: 800 mg via MN, 800 mg via AP, or 400 mg via PDDS. BAY 41-6551 levels were measured in urine and tracheal aspirates. The PDDS Clinical demonstrated the greatest delivery efficiency (approximately 60%) to the lungs and was, therefore, selected for future clinical studies.

All treatments were considered by the investigator to be well tolerated. Three patients experienced wheezing. None of the episodes of wheezing were accompanied by significant changes in heart rate or widening of the peak-to-plateau difference in airway pressure, a measure of airways resistance, and none required treatment interruption. There were no serious drug- or device-related AEs.

A Phase II study (AMIK-04-02) of aerosolized BAY 41-6551 in intubated and mechanically-ventilated patients with VAP, HAP, or HCAP has also been completed. Eligible patients were randomized in a 1:1:1 fashion to receive either aerosolized BAY 41-6551 (400 mg or 800 mg) or placebo q 12 h for a period of 7 to 14 days. Sixty-nine patients were enrolled in this multicenter, multinational study, with 67 patients receiving at least one dose of study medication. Pharmacokinetic sampling for BAY 41-6551 levels in tracheal aspirates, serum, and urine were obtained on Day 1 and Day 3 during the treatment period. Efficacy and safety variables were also measured. A total of 25 serious AEs (SAEs) were reported. One SAE was classified by the Principal Investigator (PI) as possibly related to study medication. Upon unblinding, this patient had been assigned to the placebo group. No SAEs were reported as probably related to study medication or to the PDDS Clinical regardless of treatment group. Based on the results of this trial the dose of 400 mg (amikacin as a free base) every 12 hours was chosen for further development in Phase III.

Further details on the five clinical studies completed with BAY 41-6551 can be found in the Investigator's Brochure^{18, 41}

6. Study Objectives - amended

¹⁹The study objective is 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. The primary efficacy variable is Survival as defined

¹⁸ Removed IB version and date per Amendment 6

¹⁹ Paragraph revised per Amendment 6 and 8

in Section 8.2. The secondary objectives are to evaluate the superiority of aerosolized BAY 41-6551 versus aerosolized placebo in pneumonia-related mortality to the Late Follow-up (LFU) visit, the Early Clinical Response at Day 10, the days on ventilation through the LFU visit, and the days in the ICU assessed at the LFU visit.

7. Investigators and Other Study Participants - amended

²⁰The ^{PPD} [REDACTED] The role of the coordinating investigator has been assigned to Michael S. Niederman, MD, New York-Presbyterian University Hospital of Columbia and Cornell, ^{PPD} [REDACTED]

Bayer will utilize an independent Data Monitoring Committee (DMC) to oversee this Phase III trial to ensure the ongoing safety of patients participating in the studies. The DMC will regularly review the safety data of enrolled patients, including all-cause mortality and safety signals, as well as the continuing scientific merit of the trials. The DMC can only recommend stopping the trial early due to negative safety findings. Bayer and the CRO study staff will remain blinded throughout all DMC activities. The DMC will be comprised of a minimum of two clinicians experienced in the field of clinical research, a clinician with expertise in pulmonology and at least one statistician knowledgeable in statistical methods for clinical trials. Each committee member will be screened for evidence of an absence of serious conflicts of interest. The operation of the DMC will be governed by a charter that will describe the group's frequency of meetings, procedures (including, but not limited to, periodic safety monitoring), and requirements for reporting its observations to the sponsor.

²⁰ SponsorPer Amendment 5

²¹ Updated affiliation with Amendment 6

Bayer will utilize an independent Adjudication Committee for the evaluation of the secondary variable, pneumonia-related mortality. The Adjudication Committee will be comprised of 3 clinicians experienced in the field of clinical research and anti-infective drug products. Each committee member will be screened for evidence of an absence of serious conflicts of interest. The operation of the Adjudication Committee will be governed by a charter.²²

In brief, the adjudication committee will review all deaths to determine the subset of deaths that are pneumonia-related. These pneumonia-related deaths should more likely be influenced by superior antibacterial treatment than pneumonia-unrelated deaths. The pneumonia-related death evaluation will be based on the death being plausibly related to:

- (1) pulmonary infection (example, pneumonia)
- (2) spread (metastasis) of infection (example, septicemia, septic shock)
- (3) complications related to respiratory function (example, respiratory distress)

The Adjudication Committee will have a single binary decision: pneumonia-related death: yes/no

All other study personnel, including the contract research organization (CRO) and central laboratories, not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center's investigator site file.

Whenever the term 'the investigator' is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained and delegated individual of the investigational site.

The principal investigator of each center must sign the protocol signature sheet before patient recruitment may start at the respective center. Likewise, all protocol amendments/integrated protocols must be signed and dated by the principal investigator before coming into effect at the respective center.

A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the sponsor study file.

The global sponsor of this study is identified on the title page of this protocol. If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature pages.

8. Investigational Plan

8.1 Study Design - amended

This is a Phase III, prospective, randomized, double-blind, placebo-controlled, multicenter, multinational study designed to show that aerosolized BAY 41-6551 400 mg (amikacin as free base) every 12 hours is more effective than placebo (aerosolized normal saline), as

²² Paragraph added per Amendment 6

adjunctive therapy to IV antibiotics, in intubated and mechanically-ventilated patients with Gram-negative pneumonia. The safety and tolerability of aerosolized BAY 41-6551 and the microbiological endpoints will also be evaluated. Patients who are extubated before completing the full course (10 calendar days if the first dose is administered in the AM or 11 calendar days if the first dose is administered in the PM [20 doses, Section 8.2]) of aerosol therapy will be continued on aerosolized BAY 41-6551 with the handheld adaptor. All patients will receive standard of care IV antibiotic therapy with consideration to include 2 antibiotics as per the ATS/IDSA Guidelines⁵. The doses in the guidelines are the minimum doses to be used in patients with normal renal and hepatic function. Intravenous antibiotic treatment will be administered during the entire period of aerosol treatment.²³

The study will be conducted at approximately 130 study centers in North America, South America, Asia Pacific, and Europe.²⁴

8.2 Study Plan - amended

Patients who have met all of the inclusion criteria and none of the exclusion criteria will be stratified by geographic region (or country) and disease severity using the Acute Physiology and Chronic Health Evaluation (APACHE II) score (Stratum I: APACHE II score < 20; Stratum II: APACHE II score ≥ 20) and randomized in a 1:1 ratio to one of two treatment groups: standard of care IV antibiotics with aerosolized BAY 41-6551 400 mg (amikacin as a free base) every 12 hours or standard of care IV antibiotics without aerosolized BAY 41-6551 (aerosolized placebo every 12 hours). The APACHE II score (Section 15.5) that will be used to stratify the patient is the score calculated at the time the patient is evaluated for entry into the study and a diagnosis of Gram-negative pneumonia is considered. Values used to calculate the APACHE II score (e.g. temperature, WBC counts, etc.) may be obtained at any time during the 48-hour screening period²⁵. Regardless of the treatment group, the duration of all therapy will be 10-12 full days, as described.

Patients will receive 20 doses of aerosol treatment at 12-hour intervals. Twenty doses of aerosol treatment correspond to 10 calendar days. When aerosol treatment begins with a “morning dose (AM)” the last dose (“evening dose” [PM]) will be given on the tenth day. Alternatively, if the first dose of aerosol treatment is an “evening dose” (and thus only one dose can be given on the first calendar day) the last aerosol treatment will be given as a “morning dose” on the eleventh calendar day.

Aerosolized study drug treatment and IV antibiotic treatment will both be administered for 10 full days. Both treatments will be administered in parallel. However, the protocol allows beginning empiric IV antibiotic treatment for Gram-negative pneumonia 0-48 hours before start of aerosolized study drug (Section 8.3.2). As a result, IV antibiotic therapy may extend

²³ Paragraph revised with Amendments 5, 6 and 8

²⁴ Per Amendment 5

²⁵ Per Amendment 5

up to 12 days total dosing. Every effort should be made to start study drug as close as possible to initiation of systemic antibiotic therapy.²⁶

Missing doses of inhaled study drug will not extend the treatment period of 10 calendar days.

Aerosolized therapy will be administered via the PDDS Clinical placed in a ventilator circuit (when the patient is intubated and mechanically-ventilated) or when the patient has been extubated and removed from mechanical ventilation via the handheld adaptor.

Patients will be started empirically on study drug therapy based on clinical signs of pneumonia and known or suspected²⁷ presence of Gram-negative organisms by either Gram stain or culture of pre-therapy respiratory secretions (eg, acceptable tracheal aspirate [TA], bronchoalveolar lavage [BAL], mini-BAL, and /or protected specimen brush [PSB]). The Gram stain results may be disregarded if Gram-negative pneumonia is clinically suspected or confirmed by culture.²⁸ Aerobic blood cultures will also be obtained.

During the course of therapy for Gram-negative pneumonia, respiratory secretions, when available, will be collected via tracheal aspirate suctioning and semi-quantitatively or quantitatively cultured on Days 3, 5, 7, 10, 17, and 28. Patients who are not producing sputum should not have sputum induced.²⁹

All assessments at Day 10/11 (20 doses) should be done after the last dose of aerosolized treatment.

³⁰The Test-of-Cure (TOC) visit will be conducted on Day 17-19 of the study. The late follow-up (LFU) visit will be conducted on Day 28-32 of the study. Survival will be evaluated through the LFU visit.³¹ If available, respiratory secretions will be obtained, cultured, and evaluated for the emergence of resistance to study drug therapy among baseline organisms.

³²The primary efficacy variable of the study is Survival in the mITT population through the LFU visit.

Local microbiology laboratories will perform Gram stains, identify organisms to genus and species (this information will be recorded in the case report form [CRF]) and when performing susceptibility testing will include amikacin in the sensitivity panel. The local microbiology laboratories will send a slide (air dried and not stained) of the clinical specimen (examples tracheal aspirate, sputum) to the Central Microbiology Laboratory. Instructions for preparing and shipping the slide will be provided in the investigator Manual for Microbiology. Subculture(s) of all identified pathogens that are considered clinically relevant

²⁶ Per Amendment 5

²⁷ Per Amendment 5

²⁸ Per Amendment 5

²⁹ Per Amendment 5

³⁰ Per Amendment 8

³¹ Per Amendment 6

³² Revised with Amendments 5, 6 and 8

will be sent to the Central Microbiology Laboratory. Instructions for shipping the subcultures will be provided in the investigator Manual for Microbiology.

The Central Microbiology Laboratory will execute the Gram stain and record the findings. The sub-cultures of the pathogens will be identified to genus and species, and susceptibility testing will be performed. Specific instructions will be provided in the Central Microbiology Laboratory Manual. The results of all Gram stain readings, cultures and susceptibility testing will be recorded by the Central Microbiology Laboratory and used by the sponsor for reporting purposes in the final Clinical Study Report. The local microbiology laboratory results will be used by the investigators for clinical decision making. Local microbiology results will not be used by the sponsor for reporting purposes.

8.3 Selection of Study Population - amended

³³Patients of age 18 and older, who are hospitalized, have pneumonia suspected or confirmed to be caused by Gram-negative organisms, and who are intubated and mechanically-ventilated will be selected for this study. In all patients where the pathogen is suspected of being Gram-negative, it should be confirmed as soon as culture results are available. Patients with microbiologically-confirmed pneumonia are those who have a Gram-negative organism cultured from an appropriate respiratory tract specimen.

The patient must meet all of the inclusion criteria and none of the exclusion criteria to participate in this study. Approximately 724 patients will be randomized 1:1 in the 2 Phase III studies (13084 and 13085; study 13085 is being conducted in different countries; the protocols are identical with the exception that study 13085 has a pharmacokinetic sub-study) to receive either BAY 41-6551 400 mg (amikacin as free base) aerosolized every 12 hours or aerosolized placebo every 12 hours in addition to ATS/IDSA-guided IV therapy to allow for completion of at least 472 evaluable patients (mITT) in the primary efficacy analysis.

8.3.1 Inclusion Criteria - amended

A patient must meet all of the following inclusion criteria to be eligible to participate in the study:

- 1) Males and non-pregnant, non-lactating females, 18 years of age or older. For females of child-bearing potential, one of the following medically acceptable contraceptive methods must be used or they agree to abstain from heterosexual intercourse while participating in the study. One or more of these methods should be used during the study and continue for 30 days after completion of the antibiotic therapy.
 - a. Double-barrier methods of contraception (eg, condoms plus spermicidal foam)
 - b. Intrauterine contraceptive device
 - c. Approved pharmaceutical contraceptive product (eg, birth control pills or patches, long-term injectable or implantable hormonal contraceptive)

³³ Section revised with Amendments 5 and 6

- 2) Intubated and mechanically-ventilated (patients who have had a tracheostomy may be considered as possible study participants as long as they are being mechanically ventilated)
- 3) Diagnosis of pneumonia defined as presence of a new or progressive infiltrate(s) on chest radiograph
- 4) Presence of Gram-negative organism(s) indicated by:
 - a) Gram-stain OR
 - b) Culture of pre-therapy respiratory specimen (eg, acceptable TA, BAL, mini-BAL, PSB) OR
 - c) Suspected Gram-negative pathogen based on local surveillance data and medical history. Local surveillance data reflects the local patterns of bacterial prevalence and antibiotic resistance. Consideration should be given to the recent incidence of infections with Gram-negative organisms in the hospital ³⁴
- 5) *Criterion deleted per Amendment 5*
- 6) Impaired oxygenation (within 48 hours³⁵ prior to screening): a $\text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mmHg}$ ³⁶
- 7) CPIS ≥ 6 (Section 15.3)
- 8) The presence of a MDR organism in a pre-therapy respiratory specimen OR ³⁷ at least two risk factors for MDR organisms (MDR organism: an organism resistant to representative agents in two or more of the following antibiotic classes - beta-lactams, including penicillins, cephalosporins, and monobactams; carbapenems; fluoroquinolones; and aminoglycosides):
 - a) Antimicrobial therapy in the preceding two weeks
 - b) Current hospitalization ≥ 5 days
 - c) High frequency ($> 10\%$) of antibiotic resistance in the community or in the specific hospital unit
 - d) Immunosuppressive disease and/or therapy
 - e) Presence of the risk factors for HCAP
 - Hospitalization for two days or more in the preceding 90 days
 - Residence in a nursing home or extended care facility

³⁴ Per Amendment 5

³⁵ Corrected with Amendment 6 (erroneously said 24 hours)

³⁶ Per Amendment 5

³⁷ Per Amendment 5

- Home infusion therapy (including antibiotics)
 - Chronic dialysis within 30 days
 - Home wound care
 - Family member with multidrug-resistant pathogen
- 9) Be willing and able to give written informed consent. If the patient is unable to give written informed consent, the patient's authorized³⁸ representative may provide written consent as approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

8.3.2 Exclusion Criteria - amended

A patient who meets any of the following exclusion criteria will be excluded from study participation:

- 1) A history of hypersensitivity to amikacin or other aminoglycosides
- 2) Has received antibiotic therapy for Gram-negative pneumonia for greater than 48 hours³⁹ at the time of study drug administration. There should be as minimal a time delay as possible between randomization and first dose of study drug but up to 48 hours will be acceptable

Exceptions: Systemic antibiotic therapy for more than 48 hours for Gram-negative pneumonia prior to randomization is permitted if the infection is caused by pathogens that are resistant to the antimicrobial agent(s) used, or the patient's pneumonia is worsening. The evidence for "worsening of pneumonia" should be recorded⁴⁰.

- 3) Has primary lung cancer (including patients with small cell lung carcinoma/non-small cell lung carcinoma and patients with unknown histology) or another malignancy metastatic to the lungs or other known endobronchial obstructions. *Exception:* Note that patients with complete resection of non-small cell lung carcinoma are eligible for the study.
- 4) Known or suspected active tuberculosis, cystic fibrosis, human immunodeficiency virus (HIV) infection with CD 4 count < 200 cell/mm³ (HIV testing is not required as part of this protocol), or invasive fungal infection of the lung, lung abscess, or empyema
- 5) Known or suspected bacteremia secondary to *Staphylococcus aureus*
- 6) Known or suspected neuromuscular disorders such as myasthenia gravis or parkinsonism

³⁸ Per Amendment 5

³⁹ Per Amendment 5

⁴⁰ Per Amendment 5

- 7) Has had a stroke within five days. Additionally, patients with stroke in the acute or sub-acute phase ⁴¹ should not be enrolled if at least one or both of the following apply:
 - a) There is an increased risk of fatal brain edema as indicated by a history of hypertension or heart failure, major early computed tomography (CT) hypodensity exceeding 50% of the middle cerebral artery territory, and/or involvement of additional vascular territories.
 - b) There is indication for deterioration based on comparison of patient's neurological condition within six hours of planned study drug dosing and patient's neurological condition two days before, judged by applying the National Institute of Health (NIH) Stoke Scale (Section 15.4).
- 8) A positive urine and/or serum beta-human chorionic gonadotropin (β -hCG) pregnancy test
- 9) Burns greater than 40% of total body surface area
- 10) Patients with a serum creatinine > 2 mg/dL (177 μ mol/L)

Exception: Patients with a serum creatinine > 2 mg/dL (177 μ mol/L) and being treated with continuous renal replacement therapy (continuous veno-venous hemofiltration [CVVH] and continuous veno-venous hemofiltration with dialysis [CVVH-D]) or daily hemodialysis will receive the aerosol study drug treatment (Section 8.4.6.1).

- 11) Neutropenia (Screening absolute neutrophil count [ANC] $< 10^3$ neutrophils/mm³)
- 12) Has been on mechanical ventilation for > 28 days (ie, current event should not be more than 28 continuous days). A patient is not considered extubated if cessation of mechanical ventilation ⁴² lasts less than 24 hours.
- 13) Is participating in or has participated in other investigational interventional studies within the previous 28 days
- 14) The risk of rapidly fatal illness and death within 72 hours, or any concomitant conditions not related to VAP that, in the opinion of the investigator, precludes completion of study evaluations and the course of therapy.
- 15) Stem cell transplantation
- 16) Patients with documented Legionella infection (Legionella pneumonia)
- 17) Has an APACHE II score < 10
- 18) Previous assignment to treatment during this study

⁴¹ Per Amendment 5

⁴² Per Amendment 5

- 19) Close affiliation with the investigational site; e.g. a close relative of the investigator, dependent person (e.g. employee or student of the investigational site)
- 20) Patients receiving veno-venous extracorporeal circulation membrane oxygenation (V-V ECMO) ⁴³

8.3.3 Discontinuation of Patients

Patients may prematurely discontinue study drug and/or prematurely discontinue or terminate from the study for a number of reasons. The reason(s) for premature discontinuation or termination should be clearly stated in the CRF.

A follow-up contact will be arranged as appropriate.

At the time of discontinuation, every effort should be made to ensure all procedures and evaluations scheduled for the final study visit are performed.

8.3.3.1 Reasons for Premature Discontinuation of Study Drug - amended

Since study drug is provided only as an adjunctive therapy and not the primary treatment for the patient's Gram-negative pneumonia, every effort should be made to allow patients to complete a full course of inhaled study drug to determine the impact of adjunctive therapy on the course of Gram-negative pneumonia. However, several reasons may exist to discontinue study drug.

- AE(s)
- Absence of a Gram-negative organism in a pre-therapy respiratory culture ⁴⁴
- Clinical failure (ie, lack of therapeutic effect)
- Non-adherence to study regimen
- Death
- Lost to follow-up
- Withdrawal of consent

Patients who prematurely discontinue study drug should have a Premature Withdrawal Visit at the time of discontinuation and continue to be followed for safety through the Late Follow-Up Visit.⁴⁵ The disposition of patients who are prematurely discontinued is listed in Section 11.3.⁴⁶

⁴³ Per Amendment 5

⁴⁴ Per Amendment 5

⁴⁵ Per Amendment 5

⁴⁶ Per Amendment 6.

8.3.3.2 Reasons for Premature Discontinuation from the Study

- Lost to follow-up
- Withdrawal of consent
- At the specific request of the sponsor

8.3.3.3 Premature Termination of Study/Closure of Center

The sponsor has the right to close this study, and the investigator/sponsor has the right to close a study center, at any time, although this should occur only after consultation between involved parties. The IEC/IRB must be informed. Should the study/center be closed prematurely, all study materials (except documentation that has to remain stored at the site) must be returned to the sponsor. The investigator will retain all other documents until notification is given by the sponsor for destruction.

8.4 Treatments

8.4.1 Treatments to be Administered - amended

⁴⁷Treatment will consist of standard of care IV antibiotics for intubated patients with Gram-negative pneumonia with consideration to include 2 antibiotics as per the 2005 ATS/ IDSA Guidelines, plus aerosolized BAY 41-6551 or aerosolized placebo (Section 8.2). If the patient develops a new infection, other than pneumonia, while on the aerosol treatment the patient will continue in the study.

Each inhalation or aerosol dose will be administered via the PDDS Clinical (instruction manual provided). If a patient is subsequently extubated, the aerosol treatment will be continued via the handheld adaptor for the remainder of the 10 full days of treatment course. Extending the IV antibiotic therapy beyond the aerosolized therapy might be necessary if in the opinion of the investigator, the patient continues to have clinical signs and symptoms of pneumonia. The clinical signs and symptoms of pneumonia will be documented on the CRF as will the reason(s) for continuation of IV treatment past the treatment period. Aerosol treatment will not extend beyond 10 full days corresponding to 20 doses (Section 8.2).

The administration of aerosolized antibiotics other than the aerosol study medication is prohibited.

The use of an IV aminoglycoside during the treatment period will be permitted; however, the only aminoglycoside allowed will be amikacin. This will simplify aminoglycoside trough serum level monitoring, if an IV aminoglycoside is used with the aerosol study drug. The monitoring of a single aminoglycoside (amikacin) will allow for safer use of IV therapy, if IV aminoglycoside therapy is required.

Tobramycin, gentamicin, and netelmicin will not be permitted as part of IV antibiotic therapy. This is a slight deviation from the 2005 ATS/IDSA guidelines and has been instituted in this protocol as a safeguard for patients.

⁴⁷ Section revised per Amendments 5 and 6

8.4.1.1 Antibiotic Selection

8.4.1.1.1 Initial Empiric Antibiotic Therapy - amended

In cases where specific bacterial pathogens from the respiratory tract have not yet been positively identified⁴⁸, the selection of the initial IV antibiotic regimen will be empiric and based on several factors including the patient's allergy history, previous antibiotic therapy (within the past 2 weeks), risk factors for MDR pathogens, anticipated AEs, and hospital antibiogram data. The decision on specific antibiotics to use for initial empiric combination therapy will be that of the investigator; however consideration should be given to include two (2) antibiotics, as per the 2005 ATS/IDSA Guidelines, for treating patients at risk for MDR Gram-negative pathogens (Table 1, Table 2, and Table 3 below for further guidance). Bearing in mind these Guidelines, empiric antibiotic therapy should be chosen to have activity against common circulating pathogens in the setting where the patient is being treated based on local resistance patterns. If the susceptibilities of the infecting Gram-negative pathogens are known at the time that the patient is randomized, then IV antibiotics may be targeted accordingly.

8.4.1.1.2 HAP, VAP, or HCAP in Patients with Late Onset Disease or Risk Factors for MDR Pathogens and All Disease Severity

Patients at risk for infection with *Pseudomonas aeruginosa*, *Acinetobacter* species, *Klebsiella pneumoniae*, *Enterobacter* species, and methicillin-resistant *Staphylococcus aureus* (MRSA) should initially receive combination therapy that can provide a broad spectrum of coverage to minimize the potential for initial inadequate antibiotic treatment. In the therapy of suspected pseudomonal infection, therapy should include a selected β -lactam plus either an antipseudomonal quinolone or an aminoglycoside. (Note: The only IV aminoglycoside permitted in this protocol is amikacin.) The choice of agents should be based on factors mentioned above in Section 8.4.1.1.1 and not repeat the same antimicrobial class, if possible.

⁴⁸ Per Amendment 5

Table 1: Initial Empiric Antibiotic Therapy – For Patients With Late-Onset Disease or Risk Factors for MDR Pathogens

Potential Pathogens	Recommended Antibiotic ^a
<u>MDR Pathogens</u>	Antipseudomonal cephalosporin (cefepime, ceftazidime) Or
<i>Pseudomonas aeruginosa</i>	Or
<i>Klebsiella pneumoniae</i> (Extended Spectrum Beta-Lactamase [ESBL]+) ^b	Antipseudomonal carbapenem (imipenem or meropenem) Or
<i>Acinetobacter</i> species ^b	β-Lactam/β-lactamase inhibitor (piperacillin–tazobactam) Plus Antipseudomonal fluoroquinolone ^c (ciprofloxacin or levofloxacin) Or
	Aminoglycoside (amikacin) Plus
Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	Linezolid or vancomycin ^d

MDR = multidrug-resistant.

a – Proper/adequate initial doses noted in [Table 2](#). Initial antibiotic therapy should be adjusted or streamlined on the basis of microbiologic data and clinical response to therapy.

b – If an ESBL+ strain, such as *K. pneumoniae*, or an *Acinetobacter* species is suspected, a carbapenem is a reliable choice.

c - The frequency of penicillin-resistant *S. pneumoniae* and multidrug-resistant *S. pneumoniae* is increasing; levofloxacin or moxifloxacin are preferred to ciprofloxacin and the role of other new quinolones, such as gatifloxacin, has not been established

d - If MRSA risk factors are present or there is a high incidence locally.

This table was modified from Table 4 of the 2005 ATS/IDSA Guidelines (5).

8.4.1.1.3 Initial Intravenous, Adult Doses of Antibiotics

Table 2: Initial Intravenous, Adult Doses of Antibiotics for Empiric Therapy

Antibiotic	Dosage ^a
Antipseudomonal cephalosporin	
Cefepime	1–2 g every 8–12 h
Ceftazidime	2 g every 8 h
Carbapenems	
Imipenem	500 mg every 6 h or 1g every 8 h
Meropenem	1 g every 8 h
β-Lactam/β-lactamase inhibitor	
Piperacillin–tazobactam	4.5 g every 6 h
Aminoglycosides	
Amikacin	20 mg/kg per d ^b
Antipseudomonal quinolones	
Levofloxacin	750 mg every d
Ciprofloxacin	400 mg every 8 h
Vancomycin	15 mg/kg every 12 h ^c
Linezolid	600 mg every 12 h

a - Dosages are based on normal renal and hepatic function.

b - Trough levels for amikacin should be less than 4–5 µg/mL.

c - Trough levels for vancomycin should be 15–20 µg/mL.

This table was reproduced from Table 5 of the 2005 ATS/IDSA Guidelines (5).

The armamentarium for treating *Acinetobacter* infections is limited because of resistance to many classes of antibiotics. The most consistently effective antibiotics are the carbapenems (imipenem), the sulbactam component of ampicillin-sulbactam⁴³ and the polymyxins.⁴⁴ If susceptibility testing confirms the microbiological activity of the carbapenems, ampicillin-sulbactam, or polymyxins (eg, colistin sulphomethate sodium) the IV dosage of these agents in adults with normal renal function is shown in [Table 3](#).

Table 3: Intravenous, Adult Doses of Antibiotics for Therapy of HAP, Including VAP, and HCAP in Patients With *Acinetobacter* species (adapted from ATS/IDSA 2005 [5])

Antibiotic	Dosage
Carbapenem	
Imipenem	500 mg every 6 h or 1g every 8 h
β-Lactam/β-lactamase inhibitor	
Ampicillin-sulbactam	1.5 g – 3.0 g q 6 h
Polymyxin	
Colistimethate for Injection	2.5 mg/kg – 5.0 mg/kg q 6-12 h

8.4.1.1.4 Adjustment of Empiric Intravenous Antibiotic Therapy - amended

It is not uncommon for the initial empiric therapy recommendations to require adjustment once the results of respiratory tract and blood cultures become available. Therapy can often be de-escalated (fewer antibiotics) or additional agents included based on the identity of specific pathogens, their susceptibility to specific antibiotics, and the patient’s clinical condition.

With the exception of patients receiving combination therapy with IV amikacin (the only IV aminoglycoside permitted by protocol), an adjustment to empiric antibiotics is permitted under the following circumstances.

The following instructions are intended to provide the investigator with guidance on adjusting antibiotic therapy after the initiation of IV empiric therapy:

- Adjustment to initial, IV, empiric therapy should take place within the first 96 ⁴⁹ hours after the initiation of empiric therapy or as soon as initial culture and susceptibility results are available
- Decisions on antibiotic(s) which should be added, continued or discontinued as part of maintenance therapy will be based on:
 - Organism(s) identified
 - Results of susceptibility testing
 - An evaluation of the patient's clinical signs and symptoms (eg, fever, white blood cell [WBC] count, tracheal secretions/purulence, chest radiograph, oxygenation) of pneumonia
 - An evaluation of the patient's renal and hepatic function and the patient's drug allergy history
 - It is very possible that the dose of initial empiric therapy may need to be modified based on improving or worsening renal or hepatic function. Adjustment(s) in antibiotic dosing based on renal or hepatic function would not result in the patient being evaluated as a Clinical Failure
- Further adjustments to maintenance antibiotic therapy are not permitted during the remaining treatment unless the patient is failing antibiotic treatment for pneumonia, in which case the patient would be considered a failure by the Investigator Assessment (not by the primary endpoint evaluation of Survival).⁵⁰

Exception: Patients receiving combination therapy with IV amikacin can have maintenance therapy adjusted a second time only to discontinue IV amikacin after 5 to 7 days if the patient is responding to therapy (eg, temperature decreasing, WBC count decreasing, tracheal secretion volume/purulence decreasing, chest radiograph shows no progression of infiltrate, etc) and in the interest of patient safety (adapted from ATS Guidelines, 2005)

- Refer to the Treatment Algorithm in Section 15.9 for further guidance on adjusting antibiotic therapy after the initiation of IV empiric therapy.

⁴⁹ Per Amendment 5

⁵⁰ Per Amendment 6 and 8

8.4.2 Identity of Investigational Products

For this study, BAY 41-6551 inhalation solution will be supplied to clinical sites as a preservative-free sterile solution, which has been labeled for clinical study use.

Active Ingredient:	Amikacin sulfate 1:1.8
Pharmacologic Class:	aminoglycoside antibiotic
Molecular Formula:	$C_{22}H_{43}N_5O_{13} \cdot 1.8 H_2SO_4$
Molecular Weight:	762.15
Route of Administration:	aerosol/inhalation
Storage:	2°C to 8°C (36°F to 46°F)

⁵¹The active ingredient will be obtained from ACS Dobfar (Bergamo, Italy) and the BAY 41-6551 inhalation solution will be manufactured by Bayer AG (Leverkusen, Germany). Each single-use vial has a filling volume of 3.6 mL. This fill volume of 3.6 mL is equivalent to the BAY 41-6551 solution containing 450 mg of amikacin free base at a concentration of 125 mg/mL to ensure an extractable volume of 3.2 mL. The 3.2 mL extractable volume is equivalent to 400 mg amikacin free base aerosolized. BAY 41-6551 inhalation solution appears as a clear, colorless to slightly yellowish solution. Other excipients or components of the solution include: hydrochloric acid, sodium hydroxide, water for injection, and nitrogen.

A placebo saline solution for inhalation was developed. The saline solution contains water for injection and sodium chloride.

The formulations will be packaged in a 6-mL brown glass vial (type 1 glass) with a gray chlorobutyl teflon-coated stopper and have a filling volume of 3.6 mL. A brown glass vial was chosen for light protection reasons. Teflon-coated stoppers are inert and generally compatible with aqueous solutions.

Medication will be labeled according to the requirements of local law and legislation. Label text will be approved according to agreed Bayer procedures, and a copy of the labels will be made available to the study site upon request.

All blinded medication will be labeled according to the concentration of amikacin free base (125 mg/ml) in BAY 41-6551 Solution (Amikacin Inhalation Solution). Furthermore, all stated dosages of BAY 41-6551 will refer to the corresponding amikacin free base.

8.4.3 Method of Assigning Patients to Treatment Groups - amended

All patients who meet the enrollment criteria will be stratified based on geographic region (or country)⁵² and disease severity (as determined by the APACHE II score calculated at the time the patient is evaluated for entry into the study and a diagnosis of Gram-negative pneumonia is considered):

- Stratum I: APACHE II score < 20 (mild to moderate disease severity)

⁵¹ Per Amendment 8

⁵² Per Amendment 5

- Stratum II: APACHE II score ≥ 20 (severe disease)

Following stratification, patients will be randomized 1:1, in a blinded fashion, to receive either aerosolized BAY 41-6551 400 mg (amikacin as free base) every 12 hours as adjunctive therapy to IV antibiotics or aerosolized placebo (normal saline) every 12 hours as adjunctive therapy to IV antibiotics.

8.4.4 Selection of Doses in the Study

The dose of study drug is 400 mg (amikacin as free base) BAY 41-6551 or 3.2 mL of placebo every 12 hours administered by inhalation (Section 5.4.2).

8.4.5 Administration and Dosing Regimen - amended

Dosing of BAY 41-6551 by inhalation will be every 12 hours for ten full days according to Table 4. All investigators should be aware that 400 mg every 12 hours dose of aerosolized BAY 41-6551 refers to the quantity of amikacin free base in BAY 41-6551 Solution (Amikacin Inhalation Solution) delivered from the extractable volume of 3.2 mL and that all blinded medication will be labeled according to the concentration of amikacin free base (125 mg/mL) in BAY 41-6551 Solution (Amikacin Inhalation Solution). Aerosolized therapy will begin within 48 hours⁵³ of the initiation of IV antibiotics for Gram-negative pneumonia. For the purposes of this study, a day is defined as a single 24-hour period, during which two consecutive study medication treatments are scheduled. All study medication will be delivered to the ICU or the unit where the patient may be located in the hospital from the pharmacy/study staff and provided to the investigational staff in blinded vials containing an excess of liquid to ensure an extractable volume of 3.2 mL (400 mg, amikacin as free base). The staff will be instructed to remove the metal top from the vial and pour the contents of the vial into the PDDS reservoir per the Instruction Manual. If a vial of medication is opened, the entire contents will be poured into the nebulizer at the patient's bedside. In turn, the nebulizer, when filled and the cap snapped shut, cannot be reopened and is leak resistant. All, used and unused vials and any unused medication will be returned to the pharmacy/study staff for inventory. The used and unused study medication will be stored by the investigator or designee until the inventory can be confirmed by the sponsor's designee. Study medication destruction will be performed according to normal standard practice in the local country. Study medication will be destroyed by the site or by the Bayer local affiliate or its designee.

Used devices identified on the random planned return list will be inventoried and returned to the sponsor or its designee. Used devices not on the planned return list as well as unused devices will be inventoried and destroyed on site or returned to the sponsor or its designee where required by site SOP.⁵⁴

⁵³ Correction made with Amendment 6 (was erroneously 24 hours)

⁵⁴ Paragraph revised per Amendment 6

Table 4: Study Drug Administration and Dosing Regimen

Group	Route	Study Drug and Dose^a	Amount	Regimen^b
Active	Inhalation	Active Drug: 400 mg	3.2 mL	q 12 h ^c
Placebo	Inhalation	Placebo	3.2 mL	q 12 h ^c

a - Administration of the aerosol dose of study drug in both groups will be observed to monitor tolerability.

b - Serum creatinine levels should be obtained once daily and the results available and reviewed prior to the next dose.

c - q 12 h – every 12 hours

The active treatment group will consist of patients randomized to receive a daily total aerosolized dose of 800 mg (amikacin as free base) BAY 41-6551 delivered in two equal doses per aerosol treatment.

The placebo treatment group will consist of patients randomized to receive a daily total aerosolized dose of 6.4 mL placebo delivered in two equal doses per aerosol treatment.

Dosing will be administered only after the investigator or a designated Sub-investigator has reviewed the patient’s serum creatinine levels (serum creatinine levels should be obtained once daily and the results available and reviewed prior to the next dose).

8.4.6 Dose Modification

8.4.6.1 Renal Impairment - amended

Dosing for both IV and aerosol treatments may require modification based on the patient’s renal function as measured by serum creatinine and urine output. It may also be necessary to modify the dosage regimen of aerosol therapy if there is evidence of bronchospasm during administration of the aerosol drug. Dosage modifications described are not considered protocol deviations and IV therapy should follow the recommendations set forth in the approved package labeling.

Serum creatinine levels should be obtained once daily and the results available and reviewed prior to the next dose. Patients with a serum creatinine > 2 mg/dL (> 177 µmol/L), will not receive the aerosol study drug treatment. Patients with a serum creatinine > 2 mg/dL (> 177 µmol/L) and receiving continuous renal replacement therapy (CVVH and CVVH-D) or daily hemodialysis will receive aerosol study drug treatment. Intravenous therapy should be modified according to the instructions in the manufacturer’s approved product label. If the patient is receiving IV amikacin therapy, serum amikacin levels should be monitored with the objective of achieving trough serum concentrations no greater than 4-5 µg/mL.

Dosing of the aerosol therapy will be interrupted for patients with a urine output of < 0.5 mL/kg/h for two consecutive hours. If urine output falls below this level, the serum creatinine should be (re)checked immediately. Dosing of the aerosol therapy may be resumed after urine output is ≥ 0.5 mL/kg/h and the serum creatinine is ≤ 2 mg/dL (≤ 177 µmol/L). Patients on CVVH, CVVH-D or daily hemodialysis (HD) may not meet either the urine

output or the serum creatinine requirements, but should still receive their dose every 12 hours.
55

If dosing is missed for two consecutive days (four doses of aerosol therapy) because of serum creatinine or urine output measurement results, the patient will be prematurely discontinued from study medication and followed through the late follow-up visit (Day 28-32) for safety only.

8.4.6.2 Bronchospasm

If, in the opinion of the investigator or sub-investigator(s), the patient experiences an acute onset of bronchospasm, the patient may be treated prophylactically with a bronchodilator according to clinical judgment prior to each subsequent dose of aerosol treatment, and the patient may remain on study medication. If bronchospasm recurs with subsequent administrations, the patient will be prematurely discontinued from all study medication and followed through the late follow-up visit (Day 28-32) for safety only.

All episodes of bronchospasm must be documented on the AE page of the CRF noting the seriousness, start and stop date of the bronchospasm, severity, relationship to study drug and device, actions taken (including but not limited to study drug interruption or discontinuation and any concomitant [including but not limited to bronchodilators] medications used to treat the bronchospasm) and outcome of the event.

8.5 Pulmonary Drug Delivery System (PDDS Clinical)

8.5.1 Identity of Device - amended

The PDDS Clinical is a single patient, single-dose drug delivery system, designed to deliver aerosolized medication for patients during mechanical ventilation and after extubation in the course of clinical investigation. The PDDS Clinical will be used with the inline T-piece for use during mechanical ventilation of intubated patients (Section 15.2, Figure 1 and Figure 2) and in a handheld adaptor for use post-extubation (Section 15.2, Figure 3). The PDDS Clinical nebulizer/reservoir contains Nektar's Proprietary Aerosol Generator, which delivers a fine-particle aerosol.

The PDDS Clinical control module is microprocessor-driven and utilizes a pressure transducer to monitor changes in airway pressure thus to identify inspiratory time. The microprocessor delivers aerosol during the first 75% of the inspiration. Limiting aerosol formation to the first 75% of the inspiratory cycle enhances efficiency of delivery and minimizes exhaled aerosol. By contrast, the PDDS Clinical is designed to deliver approximately 50% of the nominal dose to the lungs, based on *in vitro* data for both the on-ventilator and handheld (off-ventilator) configurations (data on file, Novartis Report No. IDD061A_TESTR_699-ProdSpecStudy_01, May 2012). The dosing is approximately 20 to 55 minutes for intubated and mechanically-ventilated patients, and approximately 10 to 25 minutes in non-intubated patients. Nebulization time can vary depending on the patient's

minute ventilation and the nebulizer flow rate output. Nebulization times not within this approximate window are not considered a protocol deviation. ⁵⁶

The PDDS Clinical handheld configuration consists of a PDDS Clinical nebulizer reservoir, aerosol chamber, mouthpiece assembly (including an expiratory filter with a flow restrictor), system cable, and a control module to provide electrical signals to the nebulizer.

The handheld configuration functions in the following ways:

- The nebulizer is always on, pumping aerosol into the aerosol chamber where it accumulates until patient inspiration.
- The patient can use the handheld with a mouth piece, self-sealing anesthesia mask, or adapted for a patient that is trached and is spontaneously breathing⁵⁷
- The base of the aerosol chamber serves as a collection chamber for oxygen (if necessary).
- The accumulated aerosol bolus is delivered to the patient upon inhalation.
- Oxygen, if needed, enters the bottom of the aerosol chamber through the one-way inhalation valve followed by ambient air.
- During exhalation, the one-way inhalation valve at the bottom of the aerosol chamber is forced closed and gas expired by the patient is routed through the flow restrictor and filtered prior to introduction into the environment.
- Nebulized aerosol continues to collect in the aerosol chamber during exhalation.
- If an inspiratory effort is not detected for 12 seconds, the aerosol generating unit shuts off, therefore further minimizing environmental exposure.

In vitro environmental exposure studies have demonstrated less than 3% of the nominal dose has been detected in the expiratory limb of the ventilator circuit in the On-Vent configuration and no amikacin was detected post expiratory filter on the handheld configuration (data on file, Nektar Report No. SB 987, Jul 2008).

The PDDS Clinical control module is identified by a unique serial number.

8.5.2 Ventilator Settings

The PDDS Clinical is designed for use with standard, adult ventilator settings. An intermittent positive pressure ventilatory mode is required to activate the PDDS Clinical to deliver aerosol during inspiration (refer to the PDDS Clinical Instruction Manual).

A heat-moisture exchanger (HME) may not be used in the PDDS Clinical circuit during dosing, according to the PDDS Clinical Instruction Manual.

⁵⁶ Per Amendment 5

⁵⁷ Per Amendment 5

8.5.3 Device Supply – amended

Prior to the first aerosolized dose of BAY 41-6551, one PDDS Clinical will be dispensed. The serial numbers for the PDDS Clinical control module and the lot number of the nebulizer/reservoir will be recorded in the dispensing log. During the 10-day treatment period, one control module will be used per patient. The nebulizer/reservoir will be dispensed after each dose and the lot number recorded.

If the patient is extubated, a handheld adaptor kit will be dispensed, but the original control module will continue to be used. The patient number and dispensing date of the nebulizer reservoirs, handheld adapter kits, and On-Vent kits will also be recorded in the dispensing log at the time of dispensing.

Used devices identified on the random planned return list will be inventoried and returned to the sponsor or sponsor's designee.⁵⁸ Used devices should be cleaned as instructed in the PDDS Clinical Instruction Manual before returning them to the sponsor or sponsor's designee. Unused devices will be inventoried and returned to the sponsor or its designee or be destroyed by the site or by the Bayer local affiliate or its designee.

8.5.4 Device Replacement

Devices for intubated and non-intubated patients may be replaced at any time if there is a suspicion of malfunction, but must be replaced if the investigator suspects the device is not performing optimally for any reason.

8.5.5 Device Malfunction or Failure

If any of the devices need to be replaced, the reason(s) will be documented in the patient's device accountability record. Additional PDDS Clinical devices are provided for this purpose. The unique serial number of the new PDDS Clinical control module and lot number for the nebulizer/reservoir will be recorded in the patient's device accountability record.

For PDDS Clinical device malfunction or complaints, the sponsor or the sponsor's designee should be contacted as soon as possible and within 24 hours.

Failed devices will be inventoried and returned to the sponsor or sponsor's designee. Failed devices should be cleaned as per the PDDS Clinical Instruction Manual before returning them to the sponsor or sponsor's designee.

8.6 Blinding/Unblinding - amended

The decision to unblind is the principal investigator's. The Medical Expert is available to discuss the need to unblind any patient, and can be contacted if needed.⁵⁹

Unblinding should only occur in the event of an emergency. Investigators should note that the occurrence of a serious adverse event (SAE) should not routinely precipitate the immediate unblinding of the label. When knowledge of the study drug is essential for the

⁵⁸ Sentence revised per Amendment 6

⁵⁹ Per Amendment 5

clinical management or welfare of the patient, the investigator may unblind a patient's treatment assignment. In the event of emergency unblinding by the investigator, the sponsor must be informed as soon as possible.

For suspected, unexpected, serious adverse reactions (SUSAR) cases where the investigator has not broken the blind, the sponsor will break the blind in accordance to the Bayer HealthCare Global standard operating procedure before reporting to Health Authorities, IRBs/ECs and investigators if the SUSAR was related to the blinded treatment. The information will be maintained in the Global Pharmacovigilance database.

Any reported SAEs that refer to a failure of the expected pharmacological action, for example worsening of Gram-negative pneumonia, are not considered SUSAR cases and are therefore exempted from unblinding.⁶⁰

8.7 Prior and Concomitant Medication

Patients are excluded if they have received another experimental drug within the previous 28 days.

Concomitant or sequential use of IV, oral, or topical nephrotoxic products, particularly bacitracin, cisplatin, amphotericin B, cephaloridine, paramomycin, viomycin, polymyxin B, colistin, vancomycin, or other aminoglycoside antibiotics, except amikacin, should be avoided when possible. The investigator is referred to the Amikacin Sulfate for Injection product label for prescribing information for IV/IM amikacin administration and to the Investigators' Brochure (IB).

Concomitant therapy with potent diuretics (such as ethacrynic acid or furosemide) should also be avoided if possible.

Concomitant therapy with inhalational anesthetics (such as halothane) or neuromuscular blocking agents (such as d-tubocurarine, succinylcholine, decamethonium) should also be avoided if possible and especially in patients who are receiving aerosol therapy via the handheld device.

All other concomitant medications necessary for the health and well-being of the patient are permitted but should be recorded (using the generic name) on the CRF.

8.8 Treatment Compliance

At all appropriate assessment periods or visits, the investigator or other study personnel will note in the CRF whether treatment has been administered, as directed in the protocol, during the preceding interval. If not, the date and reason for each deviation must be recorded.

All efforts will be made to ensure that the study will be conducted in compliance with the protocol and in accordance with Good Clinical Practice (GCP).

⁶⁰ Per Amendment 5

9. Study Procedures

9.1 Schedule of Visits and Visit Specific Procedures and Assessments

9.1.1 Screening Period (48 Hours Prior to Randomization)

Potential study patients will be recruited by the study staff among hospitalized patients with a clinical diagnosis of pneumonia who have been intubated and mechanically-ventilated (patients who have had a tracheotomy may be considered as possible study participants).

Written informed consent will be obtained from the patient or an authorized representative prior to performing screening assessments. However, standard of care procedures may be used to pre-screen the patient for study eligibility provided that the appropriate evaluations are done within two days of beginning treatment with study medication.

During the Screening Period the following assessments and procedures will be performed:

- Evaluate compliance with all inclusion and exclusion criteria
- Complete medical/surgical and medication history
- Complete physical examination, including vital signs (heart rate, blood pressure, respiratory rate, temperature), height and weight. The daily maximum temperature will be recorded.
- Chest X-ray (CXR)

NOTE: the reading and interpretation of the CXR by the investigator and/or sub-investigator(s) at the Screening Visit can be used to determine the patient's eligibility for inclusion; however, the radiology report (ie, the reading and interpretation of the CXR by the Radiologist) will be the "official" reading recorded on the CRF and used for the determination of evaluability. The radiologist will remain blinded to the treatment assignment of the patient.

- Urine or serum β -hCG pregnancy test for all women of child-bearing potential. A negative test result must be received before study medication may be given. Any patient with a positive pregnancy test result at screening will be excluded from the study.
- Clinical laboratory evaluations (hematology, serum chemistry, and urinalysis) to be conducted at the local lab
- Aerobic blood cultures obtained from two separate venipuncture sites (recommended) or according to local standards
- Arterial blood gases or pulse oximetry (arterial blood gases preferred)
- A respiratory specimen (eg, TA [Section 15.7, Guidance on Tracheal Aspirate Sampling Technique], BAL, mini-BAL, or PSB) will be obtained for Gram stain, semi-quantitative or quantitative culture, and susceptibility testing.

NOTE: All respiratory specimens will be evaluated by Gram stain and rejected

for culture if the Gram stain reveals > 10 squamous epithelial cells per low powered (100 x) field.⁴²

- Pleural fluid cultures or cultures of any other material (repeated as necessary until negative), if clinically indicated
- Calculated CPIS must be ≥ 6 , (Section 15.3 - description of the CPIS used in this study and guidance on calculating a score)
- Calculate the APACHE II score
- Assessment of clinical signs and symptoms of pneumonia
- Concomitant medication use

If a patient meets all the eligibility criteria, the patient may be enrolled and randomized to study medication. The Study Flow Chart and/or Schedule of Procedures is contained in Section 15.1.

9.1.2 Treatment Period (Day 1 to Day 10) - amended

Day 1 is defined as the day the initial dose of study medication (aerosolized BAY 41-6551 or aerosolized placebo⁶¹) is given. Day 1 may be the same day as when the informed consent form (ICF) is signed, screening assessments are performed, and the patient is enrolled.

- Prior to the first dose, each patient will receive a PDDS Clinical device consisting of a control module, T-piece adaptor, alternating current/direct current (AC/DC) adaptor, air pressure feedback device, and cable (Section 8.5).
- Patients will be started on aerosolized study medication within 48 hours⁶² of IV antibiotic therapy being initiated for Gram-negative pneumonia. Patients will receive 3.2 mL of either BAY 41-6551 (400 mg [amikacin as free base]) or placebo solution every 12 hours (a window of ± 4 hours is acceptable) via the PDDS Clinical for 10 full calendar days (20 doses) (Section 8.2). If a patient is extubated during the course of treatment or has a tracheostomy and is spontaneously breathing, aerosol administration will continue via the handheld adaptor for the remainder of the treatment period.

9.1.2.1 Assessments Performed Daily - amended

Patients will have the following assessments and procedures performed daily, unless otherwise indicated, during the treatment period:

- A physical examination including vital signs
- An assessment of clinical signs and symptoms of pneumonia

⁶¹ “aerosolized” added per Amendment 6

⁶² 24 hours changed to 48 hours with Amendment 6

- Measurement of serum creatinine. Serum creatinine levels should be obtained once daily and the results available and reviewed prior to the next dose.
- Concomitant medications and AEs will be monitored and recorded.
- Collection of ventilator parameters pre- and post-dose of study drug ⁶³
- Amikacin serum level monitoring

Serum amikacin levels will be obtained for those patients receiving IV amikacin therapy. Serum level monitoring and/or dosage adjustments will be performed according to institutional guidelines or the standard of practice at the site. A serum amikacin sample should also be sent to the Central Laboratory. The Central Laboratory will not report serum amikacin levels to the investigator or sub-investigator(s).

Patients not receiving IV amikacin therapy but receiving aerosol treatment will have amikacin serum levels monitored through the Central Laboratory, therefore, a serum amikacin sample should be sent to the Central Laboratory. However, because of low systemic exposure following aerosol treatment, amikacin serum levels will **not** be reported to the investigator or sub-investigator(s).

- Measurement of serum amikacin trough level 30 minutes (\pm 15 mins) ⁶⁴ prior to each first aerosol dose of the day. ⁶⁵

9.1.2.2 Assessments Performed on Days 1, 3, 5, and 7 - amended

⁶⁵Patients will have the following assessments and procedures performed on Days 1, 3, 5, and 7 during the treatment period as indicated:

- CXR obtained

NOTE: the reading and interpretation of the CXR by the investigator and/or sub-investigator(s) at the During Treatment Visits can be used for clinical decision-making; however, the radiology report (ie, the reading and interpretation of the CXR by the radiologist) will be the "official" reading recorded on the CRF and used for the determination of evaluability. The radiologist will remain blinded to the treatment assignment of the patient.

- Clinical laboratory evaluations (hematology, serum chemistry, and urinalysis) to be conducted at the local lab
- Aerobic blood cultures obtained from two separate venipuncture sites (recommended) or according to local standards

⁶³ Per Amendment 5

⁶⁴ Per Amendment 5

⁶⁵ The measurement of serum amikacin trough level was moved from Section 9.1.2.2 to 9.1.2.1 with Amendment 6

- Arterial blood gases or pulse oximetry (arterial blood gases preferred)
- A respiratory specimen (eg, TA [Section 15.7, Guidance on Tracheal Aspirate Sampling Technique], BAL, mini-BAL, or PSB) will be obtained for Gram stain, semi-quantitative or quantitative culture, and susceptibility testing.

NOTE: All respiratory specimens will be evaluated by Gram stain and rejected for culture if the Gram stain reveals > 10 squamous epithelial cells per low powered (100 x) field.

- Pleural fluid cultures or cultures of any other material (repeated as necessary until negative), if clinically indicated
- Calculated CPIS (Section 15.3- description of the CPIS used in this study and guidance on calculating a score)

9.1.3 Post-Treatment Period (Days 10-32)

9.1.3.1 End of Therapy Visit (Day 10) - amended

The end of therapy (EOT) visit will be conducted on Day 10 or within 24 hours after completion of study drug. The Investigator Assessment of Patient Outcome will involve an evaluation of clinical signs and symptoms.⁶⁶

Patients will have the following assessments and procedures performed during the EOT visit:

- A physical examination including vital signs
- CXR obtained

NOTE: the reading and interpretation of the CXR by the investigator and/or sub-investigator(s) at the EOT visit can be used to determine the Investigator Assessment of Patient Outcome;⁶⁷ however, the radiology report (i.e., the reading and interpretation of the CXR by the Radiologist) will be the “official” reading recorded on the CRF and used for the determination of evaluability. The radiologist will remain blinded to the treatment assignment of the patient.

- Clinical laboratory evaluations (hematology, serum chemistry, and urinalysis) to be conducted at the local lab
- Arterial blood gas or pulse oximetry (arterial blood gases preferred)
- A respiratory specimen (e.g., TA [Section 15.7, Guidance on Tracheal Aspirate Sampling Technique], BAL, mini-BAL, or PSB) will be obtained for Gram stain, semi-quantitative or quantitative culture, and susceptibility testing

NOTE: All respiratory specimens will be evaluated by Gram stain and rejected for

⁶⁶ Per Amendment 6

⁶⁷ Per Amendment 6

culture if the Gram stain reveals > 10 squamous epithelial cells per low powered (100 X) field.

- Calculate CPIS (Section 15.3 – description of the CPIS used in this study and guidance on calculating a score)
- Concomitant medication and AEs will be monitored and recorded.

9.1.3.2 Test-of-Cure (TOC) Visit (Days 17 - 19) - amended

The TOC visit will be conducted on Days 17-19 of the study. The Investigator Assessment of Patient Outcome will be determined by an assessment of clinical signs and symptoms.⁶⁸

Patients will have the following assessments and procedures performed during the TOC visit:

- Complete physical examination, including vital signs and weight. In addition, the daily maximum temperature will be recorded.
- An assessment of clinical signs and symptoms of pneumonia
- CXR obtained

NOTE: the reading and interpretation of the CXR by the investigator and/or sub-investigator(s) at the TOC visit can be used to determine the Investigator Assessment of Patient Outcome;⁶⁹ however, the radiology report (ie, the reading and interpretation of the CXR by the radiologist) will be the "official" reading recorded on the CRF and used for the determination of evaluability. The radiologist will remain blinded to the treatment assignment of the patient.

- Clinical laboratory evaluations (hematology, serum chemistry, and urinalysis) to be conducted at the local lab
- Aerobic blood cultures obtained from two separate venipuncture sites (recommended) or according to local standards
- Arterial blood gas ⁷⁰
- A respiratory specimen (eg, TA [Section 15.7, Guidance on Tracheal Aspirate Sampling Technique], BAL, mini-BAL, or PSB) will be obtained for Gram stain, semi-quantitative or quantitative culture, and susceptibility testing.

NOTE: All respiratory specimens will be evaluated by Gram stain and rejected for culture if the Gram stain reveals > 10 squamous epithelial cells per low powered (100 x) field.

⁶⁸ Per Amendment 6

⁶⁹ Per Amendment 6

⁷⁰ Per Amendment 6

- Calculated CPIS (Section 15.3 - description of the CPIS used in this study and guidance on calculating a score)
- Concomitant medications and AEs will be monitored and recorded

9.1.3.3 Late Follow-Up Visit (Days 28 - 32) - amended

The LFU visit will be conducted on Days 28 – 32 of the study. Patients will be strongly encouraged to return to their study facility for their LFU visit. However, if this is not feasible all obtainable information can be collected by telephone from the patient or the patient's care giver.

The following assessments should be performed:

- Complete physical examination, including vital signs and weight. In addition, the daily maximum temperature will be recorded.
- Complete the Late Follow-Up Questionnaire (see Section 15.6)
- An assessment of clinical signs and symptoms of pneumonia
- The Investigator Assessment of Patient Outcome will be determined by an assessment of clinical signs and symptoms⁷¹
- Calculated CPIS (Section 15.3 - description of the CPIS used in this study and guidance on calculating a score)
- Concomitant medications and AEs will be monitored and recorded
- Clinical laboratory evaluations (hematology, serum chemistry, and urinalysis) to be conducted at the local lab

The following assessments should only be performed if clinically indicated.

- CXR obtained
- Aerobic blood cultures
- Arterial blood gas or pulse oximetry (arterial blood gases are preferred)
- A respiratory specimen (eg, TA [Section 15.7, Guidance on Tracheal Aspirate Sampling Technique], BAL, mini-BAL, or PSB) will be obtained for Gram stain, semi-quantitative or quantitative culture, and susceptibility testing.

NOTE: All respiratory specimens will be evaluated by Gram stain and rejected for culture if the Gram stain reveals > 10 squamous epithelial cells per low powered (100 x) field.

⁷¹ Per Amendment 6

9.2 Completion of Study

A patient is considered to have completed the study when they have completed the treatment period and both post-treatment follow-up visits (eg, TOC and LFU visit).

9.3 Follow-Up Assessments

Follow-up assessments will be obtained as needed to monitor any SAE until the event resolves or is considered to be stable and non-resolving. Hearing loss should be noted on the CRF.

9.4 Unscheduled Assessments or Visits

The investigator is responsible for monitoring patients for any treatment-related toxicity. Blood samples for clinical laboratory tests may be drawn at any time at the discretion of the investigator.

Samples obtained at unscheduled times will be sent to the local laboratory for analysis.

9.5 Premature Discontinuation / Early Withdrawal from Study - amended

Patients prematurely discontinuing or withdrawing early from the study, for whatever reason, will be asked to undergo the following evaluations at the time of discontinuation / withdrawal:

- Complete physical examination, including vital signs; in addition the daily maximum temperature will be recorded
- CXR

NOTE: the reading and interpretation of the CXR by the investigator and/or sub-investigator(s) can be used to determine the Investigator Assessment of Patient Outcome;⁷² however, the radiology report (ie, the reading and interpretation of the CXR by the radiologist) will be the "official" reading recorded on the CRF. The radiologist will remain blinded to the treatment assignment of the patient.

- Clinical laboratory evaluations (hematology, serum chemistry, and urinalysis)
- Aerobic blood cultures obtained from two separate venipuncture sites (recommended) or according to local standards
- Arterial blood gas ⁷³
- Calculated CPIS (Section 15.3 - description of the CPIS used in this study and guidance on calculating a score)
- Assessment of clinical signs and symptoms of pneumonia

⁷² Per Amendment 6

⁷³ Per Amendment 6

- A respiratory specimen (eg, TA [Section 15.7, Guidance on Tracheal Aspirate Sampling Technique], BAL, mini-BAL, or PSB) will be obtained for Gram stain, semi-quantitative or quantitative culture, and susceptibility testing.

NOTE: All respiratory specimens will be evaluated by Gram stain and rejected for culture if the Gram stain reveals >10 squamous epithelial cells per low powered (100 x) field.

- Pleural fluid cultures or cultures of any other material if clinically indicated
- Concomitant medications and AEs will be monitored and recorded

9.6 Study Measurements

The objective of this study is to evaluate the efficacy and safety of adjunctive aerosolized BAY 41-6551 in the treatment of intubated and mechanically-ventilated adult patients with Gram-negative pneumonia.

9.6.1 Efficacy Variables – amended

9.6.1.1 Primary Efficacy Variable: Survival - amended

⁷⁴The primary efficacy variable is Survival, which is determined by tabulating the cumulative mortality and survival through the LFU visit for each mITT patient. Survival (and mortality) is the only criteria evaluated for the primary endpoint, no other factors are considered other than survival status through the LFU visit.

9.6.1.2 Additional Analysis of Clinical Success - amended

⁷⁵There are three additional analyses of clinical success. These three analyses are separate from the primary endpoint. The three analyses are (1) the FNIH recommendations for an endpoint based on mortality plus septic shock, (2) the Investigator's assessment of Patient Outcome, and (3) the Composite Endpoint Evaluation (the previous Primary Endpoint).

9.6.1.2.1 FNIH Criteria - amended

⁷⁶Clinical success using FNIH recommendations is defined as mITT patients who survived through the LFU visit and did not have septic shock. Patients will be designated as having a septic shock event based on the standard medical queries (SMQ) terms tabulated as adverse events.

⁷⁴ Per Amendment 6 and 8

⁷⁵ Added per Amendment 8

⁷⁶ Added per Amendment 8

9.6.1.2.2 Investigator Assessment of Patient Outcome - amended

⁷⁷ The investigators will also assess patient outcome based on a composite endpoint. The Investigator Assessment of Patient Outcome is separate and different from the primary endpoint of Survival, which is done by using a computer algorithm based on collected data and specific criteria. The Investigator Assessment of Patient Outcome is based on the following criteria:

- CPIS assessed at baseline, Days 3, 5, 10, and the TOC visit
- All-cause mortality assessed through the TOC visit
- Systemic antibacterial use for the current episode of pneumonia beyond Day 10 (the EOT for aerosol administration)
- Antibiotic adjustments made during therapy

9.6.1.2.2.1 End of Therapy (Day 10)

⁷⁸ The Investigator Assessment of Patient Outcome will be evaluated at the EOT visit using the following terms and definition.

Investigator Assessment of Patient Outcome - Cure:

- Improvement or lack of progression of all abnormalities associated with pneumonia on chest radiograph;
- Resolution towards normal of the following components of the CPIS - tracheal secretions (volume and purulence), temperature, blood leukocytes, oxygenation ($\text{PaO}_2/\text{FiO}_2$);

NOTE: “resolution towards normal”, as used in this definition, is intended to mean that the components of the CPIS may not be within normal limits (e.g., continuing low-grade fever or leukocytosis in an ICU patient); however, in the opinion of the investigator the measure is considered not to be clinically significant in the context of resolving pneumonia.

- The patient never reached any of the early failure criteria AND
- The patient survived through the EOT visit

NOTE: All four conditions listed above must be met in order for the Investigator Assessment of Patient Outcome to be a cure.

Investigator Assessment of Patient Outcome - Failure:

- Rise in the CPIS by at least 2 points on Day 3;
- Failure of the CPIS to drop at least 1 point on Day 5;

⁷⁷ Section revised per Amendment 6 and 8

⁷⁸ Section revised per Amendment 6

- Failure of the CPIS to drop by at least 2 points on Day 10;
- Continuation of systemic antibiotics (IV or PO) for pneumonia after Day 10;
- Any further change to the Gram-negative portion of the ⁷⁹ antimicrobial regimen being used to treat pneumonia during the first 10 days, after the initial antimicrobial adjustment within the first 96 ⁸⁰ hours after the initiation of empiric therapy or as soon as initial culture and susceptibility results are available and excepting the discontinuation of aminoglycosides after 5-7 days, would be considered a Clinical Failure;

OR

- All-cause mortality by the EOT visit.

NOTE: If any one of the above conditions is met, the Investigator Assessment of Patient Outcome is a failure

9.6.1.2.2.2 Test-of-Cure (TOC) Visit (Day 17-19) - amended

⁸¹The Investigator Assessment of Patient Outcome will be evaluated at the TOC visit using the following terms and definitions:

Investigator Assessment of Patient Outcome - Cure:

- Improvement or lack of progression of all abnormalities associated with pneumonia on chest radiograph;
- Resolution towards normal of the following components of the CPIS - tracheal secretions (volume and purulence), temperature, blood leukocytes, oxygenation (PaO₂/FiO₂);

NOTE: “resolution towards normal”, as used in this definition, is intended to mean that the components of the CPIS may not be within normal limits (eg, continuing low-grade fever or leukocytosis in an ICU patient); however, in the opinion of the investigator, the measure is considered not to be clinically significant in the context of resolving pneumonia.

- The patient never reached any of the early failure criteria;
- The patient did not receive antibiotic therapy for pneumonia after 10 days; AND
- The patient survived through the TOC visit.

NOTE: All five conditions listed above must be met in order for the Investigator Assessment of Patient Outcome to be a cure.

⁷⁹ Per Amendment 5

⁸⁰ Per Amendment 5

⁸¹ Section revised per Amendment 6

Investigator Assessment of Patient Outcome - Failure:

- Rise in the CPIS by at least 2 points on Day 3;
- Failure of the CPIS to drop at least 1 point on Day 5;
- Failure of the CPIS to drop by at least 2 points on Day 10;
- Continuation of systemic antibiotics (IV or PO) for pneumonia after Day 10;
- Restarting systemic antibiotics (IV or PO) for pneumonia before the TOC (with a positive respiratory culture) visit;
- Any further change to the Gram-negative portion of the ⁸² antimicrobial regimen being used to treat pneumonia during the first 10 days, after the initial antimicrobial adjustment within the first 96 ⁸³ hours after the initiation of empiric therapy or as soon as initial culture and susceptibility results are available and excepting the discontinuation of aminoglycosides after 5-7 days, would be considered a Clinical Failure;

OR

- All-cause mortality by the TOC visit.

NOTE: If any one of the above conditions is met, the Investigator Assessment of Patient Outcome is a failure.

At Day 10 (End of Therapy), the criteria to determine whether IV antibiotics need to be continued will be an assessment of clinical signs and symptoms of pneumonia. Specifically, this evaluation will consider temperature (°C or °F), blood leukocyte (WBC) count (cells/mm³) with differential (including % neutrophils), oxygenation (PaO₂/FiO₂) (mm Hg), volume and appearance of tracheal secretions (few, moderate, large, purulent) and chest radiography (no infiltrate, patchy or diffuse infiltrate, localized infiltrate).

At Day 10, corresponding to the completion of 20 doses (EOT), patient outcome of failure will be defined as a failure to decrease the CPIS by 2 points. There may be instances at Day 10 where, if the CPIS falls by more than 2 points, there could still be reasons to continue IV antibiotic therapy and also instances where the score could fail to fall by more than 2 points and antibiotic therapy might be discontinued. In both instances of such patient outcome failure, the reasons for continuing or discontinuing antibiotic therapy will be specified in the CRF.

A patient outcome of failure will be carried through the LFU visit evaluation.

⁸² Per Amendment 5

⁸³ Per Amendment 5

9.6.1.2.2.3 Late Follow-up Visit (Days 28 – 32) – amended

⁸⁴The Investigator Assessment of Patient Outcome will be evaluated at the LFU visit. As mentioned previously, a patient evaluated at the TOC visit as a patient outcome failure will have that response carried forward to the LFU visit.

For patients who were evaluated at the TOC visit as a patient outcome cure, their clinical response will be graded as:

Continued Investigator Assessment of Patient Outcome Cure: continued resolution of clinical signs and symptoms of pneumonia and continued improvement or lack of progression of all abnormalities on chest radiograph such that additional antibiotic therapy to treat pneumonia is not required.

Relapse: reappearance of the signs and symptoms of pneumonia and worsening or progression of abnormalities on chest radiograph such that alternative antibiotic therapy is required.

9.6.1.2.2.4 Premature Discontinuation Visit - amended

⁸⁵A patient may not complete a full 10-day (20 doses) course of study drug treatment or may not reach the TOC visit (Days 17-19). These patients may prematurely discontinue therapy because they are failing study treatment and alternative antibiotic therapy is required, while others may discontinue study medication because of an AE, protocol violation or other reasons as noted in Section 8.3.3.1. Alternative antibiotic therapy may or may not be required.

For a patient outcome failure (ie, study drug therapy is discontinued because of a lack of therapeutic effect), the evaluation of the patient's clinical condition should be based on the clinical signs and symptoms of pneumonia as well as objective evidence of failure (eg, persistent fever, rising WBC count, increasing tracheal secretions, poor oxygenation, progression of infiltrate on CXR) and a measure of their CPIS. This information should be recorded on the CRF, as well as an evaluation of the patient's clinical response to study drug. In most cases, the decision to evaluate the patient as a Clinical Failure will be made after at least 72 hours of study medication, but in rare instances, the clinical course of the illness may require that study medication be discontinued prior to three days treatment and alternative antibiotic therapy started. Regardless of when the patient is prematurely discontinued, the clinical condition of the patient should be determined at the time of study drug discontinuation, recorded on the CRF, and a clinical response evaluation completed.

At the premature discontinuation visit, the patient's outcome will be assessed according to the following terms and definitions.

⁸⁴ Section revised per Amendment 6

⁸⁵ Section revised per Amendment 6

Investigator Assessment of Patient Outcome - Failure:

- Rise in the CPIS by at least 2 points on Day 3;
- Failure of the CPIS to drop at least 1 point on Day 5;
- Failure of the CPIS to drop by at least 2 points on Day 10;
- Continuation of systemic antibiotics (IV or PO) for pneumonia after Day 10;
- Restarting systemic antibiotics (IV or PO) for pneumonia before the TOC (with a positive respiratory culture) visit;
- Any further change to the antimicrobial regimen being used to treat pneumonia during the first 10 days, after the initial antimicrobial adjustment within the first 72 hours after the initiation of empiric therapy or as soon as initial culture and susceptibility results are available and excepting the discontinuation of aminoglycosides after 5-7 days, would be considered a patient outcome failure;

OR

- All-cause mortality.

NOTE: At least one of the above conditions is necessary to consider a patient a patient outcome failure.

In the case of the patient who has discontinued study drug for another reason (eg, AE, protocol violation, etc), the patient should be evaluated clinically to determine their response to treatment at the point they are discontinued. This assessment would be recorded on the CRF and include a determination of their clinical signs and symptoms of pneumonia and a measure of their CPIS.

Clinical Improvement: reduction in the severity and/or number of clinical signs and symptoms of pneumonia and alternative antibiotic therapy is considered and may or may not be initiated.

Indeterminate: not possible to determine clinical response to treatment (eg, withdrawal after less than three days of study drug therapy due to an AE). The reason(s) for an indeterminate response must be recorded on the CRF.

9.6.1.2.3 Composite Endpoint Evaluation: - amended

⁸⁶An evaluation of patient outcome based on 5 components is determined by using a computer algorithm based on collected data and specific criteria. This assessment based on 5 criteria is separate and different from the Primary Endpoint of Survival. For a patient to be evaluated as a Clinical Success for the Composite Endpoint Evaluation all the following criteria must be met:

- Systemic antibiotics (IV or PO) for pneumonia must be stopped on or before the TOC visit
- Systemic antibiotics (IV or PO) for pneumonia must not be restarted after the TOC visit
- The patient must survive through the LFU visit
- The patient must not have a reported AE of lung abscess or empyema through the LFU visit
- The patient must have stable respiratory function evaluated at the TOC visit based on the P/F ratio (see below)

Stable respiratory function:

- Patient is extubated at the TOC visit OR
- Patient is intubated at the TOC visit AND:
 - Patient has a P/F ratio > 200 at the TOC visit OR
 - Patient has a P/F ratio > 100 and ≤ 200 at the TOC visit AND:
 - Patient had a P/F ratio ≤ 200 at baseline

Unstable respiratory function

- Patient has a P/F ratio ≤ 100 at the TOC visit OR
- Patient has a P/F ratio > 100 and ≤ 200 at the TOC visit AND:
 - Patient had a P/F ratio > 200 at baseline

The outcome is Clinical Success if all 5 criteria are met. If any one of the criteria is not met, then the patient is considered a Clinical Failure. Patients who do not have a clinical assessment of success due to missing data will be considered a Clinical Failure.

9.6.2 Safety Variables

All patients who have received at least one dose of the study drug(s) will be evaluated for safety in a descriptive manner. The safety analysis will include tabulation of the type (using Medical Dictionary for Regulatory Activities [MedDRA] glossary) and frequency of all AEs.

⁸⁶ Per Amendment 8

Drug-related AEs, SAEs, premature discontinuations due to AEs will also be summarized, as well as AEs by severity, outcome, and action taken.

Incidence tables will be presented for all AEs up to seven days after the end of treatment and for SAEs, up to the Day 28 visit.

All laboratory data will be analyzed using descriptive statistics including identification of laboratory data outside normal ranges.

Rates of organ failure will also be summarized, by patient as well as by specific organ type.

⁸⁷Mortality during the treatment period, Day 15 and Day 28 visit will be summarized (This is also the primary efficacy endpoint).

9.6.2.1 Clinical Laboratory Tests

The following clinical laboratory tests will be performed (Section 15.1):

- Hematology: hemoglobin, hematocrit, WBC with differential (%), red blood cell (RBC) count, platelet count
- Chemistry: alkaline phosphatase, alanine aminotransferase/serum glutamate pyruvate transaminase (ALT/SGPT), aspartate aminotransferase/serum glutamic oxalo-acetic transaminase (AST/SGOT), bicarbonate, bilirubin (total and direct), blood urea nitrogen (BUN), calcium, chloride, cholesterol (total), creatinine, gamma-glutamyl transferase (GGT), glucose, lactate dehydrogenase (LDH), phosphorus, potassium, protein (total), sodium, triglycerides, and uric acid
- Urinalysis: appearance, specific gravity, pH, protein, ketones, bilirubin, urobilinogen, blood, nitrite, microscopic examination of sediment.

Serum creatinine levels should be obtained once daily and the results available and reviewed prior to the next dose.

The investigator will record on the laboratory report his/her medical opinion of the clinical significance of all laboratory values that are outside the laboratory reference range. The investigator will sign and date each laboratory report form. Clinically significant laboratory findings made after the start of study medication that meet the definition of an AE must be recorded on the CRF.

The investigator will provide the sponsor or sponsor's designee with a copy of each laboratory's certification and a tabulation of the normal ranges.

9.6.2.2 Bacteriological Response Assessments

Bacteriological response will be based on the results of the appropriate cultures taken before, during, and after therapy. For infections caused by two or more pathogens, the response for each organism will be assessed separately.

⁸⁷ Revised per Amendment 8

9.6.2.2.1 Test-of-Cure (TOC) Visit (Days 17-19)

The bacteriological response at the TOC visit will be graded as follows:

- **Eradication:** the absence of the original pathogen(s) at the post-treatment TOC culture of specimens from the original site of infection
- **Presumed eradication:** absence of appropriate culture material in a patient judged to be a clinical cure; he or she is unable to produce sputum and invasive procedures are not warranted
- **Persistence:** the presence of the original pathogen from the post-treatment TOC culture specimens from the original site of infection
- **Presumed persistence:** the absence of appropriate culture material in a patient judged to be a Clinical Failure and invasive procedures are not warranted
- **Superinfection:** the isolation of a new pathogen (not the original pathogen) from a specimen taken while the patient is on antibiotic therapy, signs and symptoms indicative of pneumonia are present, and there is a need for alternative antimicrobial therapy (Superinfections will not be considered microbiological failures, but will be assessed separately)
- **New infection:** the isolation of a new pathogen (not the original pathogen) from a specimen taken after the patient has completed antibiotic therapy, signs and symptoms indicative of pneumonia are present, and there is a need for alternative antimicrobial therapy
- **Indeterminate:** the bacteriological response to the study medication is not valid for any reason (eg, pre-treatment culture was negative or post-treatment culture was not obtained when material was available)

9.6.2.2.2 Late Follow-up Visit (Days 28-32)

Continued Eradication: the absence of the original pathogen(s) at the post-treatment late follow-up culture of specimens from the original site of infection.

Continued Presumed Eradication: absence of appropriate culture material for evaluation because the patient's pneumonia has resolved clinically, he or she is unable to produce sputum and invasive procedures are not warranted.

Recurrence: the reappearance of the original pathogen(s) from a specimen taken after the TOC visit.

New infection: the isolation of a new pathogen (not the original pathogen) from a specimen taken after the patient has completed antibiotic therapy, signs and symptoms indicative of pneumonia are present, and there is a need for alternative antimicrobial therapy.

Indeterminate: the bacteriological response to the study medication is not valid for any reason (eg, pre-treatment culture was negative or post-treatment culture was not obtained when material was available).

9.7 Data Quality

Monitoring and auditing procedures defined/agreed to by the sponsor will be followed, in order to comply with GCP guidelines. Each center will be visited at regular intervals by a Monitor to ensure compliance with the study protocol, GCP and legal aspects. This will include on-site checking of the CRF for completeness and clarity, cross-checking with source documents, and clarification of administrative matters.

9.8 Documentation

Entries made in the CRF must be either verifiable against source documents, or have been directly entered into the CRF, in which case the entry in the CRF will be considered as the source data. The source data parameter to be verified and the identification of the source document must be documented. The study file and all source data should be retained until notification given by the sponsor for destruction.

10. Ethical and Legal Aspects

10.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Documented approval from appropriate IECs/IRBs will be obtained for all participating centers/countries prior to study start, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IEC/IRB approval must be obtained and also forwarded to the sponsor. The IEC/IRBs must supply to the sponsor, upon request, a list of the IEC/IRB members involved in the vote and a statement to confirm that the IEC/IRB is organized and operates according to GCP and applicable laws and regulations.

10.2 Ethical Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by GCP Guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s). This may include an inspection by the sponsor's representatives and/or Regulatory Authority's representatives at any time. The investigator must agree to the inspection of study-related records by the Regulatory Authority/sponsor representatives, and must allow direct access to source documents to the Regulatory Authority/sponsor representatives.

The IRBs/IECs must approve the protocol prior to the start of the study. Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator or the sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial patients without prior IEC/IRB/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution/sponsor. Any deviations from the protocol must be explained and documented by the investigator.

10.3 Regulatory Authority Approvals/Authorizations

Regulatory Authority approvals / authorizations / notifications, where required, must be in place and fully documented prior to study start.

10.4 Patient Information and Consent - amended

A core information and ICF will be provided. Prior to the beginning of the study, the investigator must have the IEC/IRB written approval/favorable opinion of the written ICF and any other written information to be provided to patients. The written approval of the IEC/IRB together with the approved patient information / ICF must be filed in the study files.

Written informed consent must be obtained before any study specific procedure takes place. Participation in the study and date of informed consent given by the patient or an authorized representative should be documented appropriately in the patient's files. In the case where the patient is unable to provide consent, the patient's legally authorized representative (LAR) (in accordance with applicable law) may provide consent for the patient. In the absence of a LAR, the investigator must seek local legal and ethical guidance to ensure that, in such cases, consent is obtained for patients in accordance with local requirements.

Under these circumstances, if the patient becomes able during their participation in the trial, information about the trial should be given to the patient and their consent to remain in the clinical research study should be obtained as soon as possible. The consent process for such patients should be clearly documented in the patient's medical records.⁸⁸

10.5 Insurance

All patients participating in the study will have insurance coverage by the sponsor, which is in line with applicable laws and/or regulations.

10.6 Confidentiality

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and / or regulations, will not be made publicly available.

Patient names will not be supplied to the sponsor. Only the patient number will be recorded in the CRF. If the patient name appears on any other document (eg, pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The patients will be informed in writing that representatives of the sponsor, IEC/IRB, or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the patient's identity will remain confidential.

The investigator will maintain a list to enable patients' records to be identified.

⁸⁸ Per Amendment 5

11. Statistical Methods and Determination of Sample Size

11.1 Statistical and Analytical Plans

11.1.1 Analysis Populations - amended

The two populations used for analysis will be the mITT population and the ITT population. These populations will be comprised of patients recruited to this study and to study 13085 (being conducted in different countries; the protocols are identical with the exception that study 13085 has a pharmacokinetic substudy). The patients will be recruited competitively between studies 13084 and 13085; there are no minimum requirements for recruitment totals in either study.⁸⁹ The mITT population is defined as all randomized patients with culture-confirmed Gram-negative bacteria who have been treated with at least one dose of study drug and have an APACHE II score ≥ 10 at the time of diagnosis of pneumonia. The ITT population is defined as all patients treated with at least one dose of study drug.

11.1.2 Analytical Plan - amended

The primary efficacy analysis will be conducted in the mITT population. The primary analysis is on the combined database, no single study analyses will be performed as part of the primary analysis.⁹⁰ Unless otherwise specified, all significance tests will be conducted using a two-sided alpha level of 0.05.

All variables collected in this study will be summarized with descriptive statistics at each assessment time. Patient disposition and demographic and baseline characteristics will be summarized descriptively for each treatment group. Demographic variables will be summarized for both the mITT and ITT populations.

Duration of treatment (the total number of doses) will be summarized descriptively by treatment group and delivery type (eg, on vent and handheld). Overall duration and duration by device type will be provided for both the mITT and ITT populations.

All safety analyses will be provided only for the ITT population.

For continuous variables, descriptive statistics will include means, standard deviations, medians, minimums and maximums. For categorical variables, frequency counts and percentages will be provided.

11.2 Determination of Sample Size - amended

⁹¹For this combined study (studies 13084 and 13085), a two group χ^2 test with a 0.05 two-sided significance level will have 81% power to detect the difference between BAY 41-6551 survival rate at LFU of 80% and Placebo survival rate at LFU of 69% when the sample size in each group is 254.

⁸⁹ Two sentences added per Amendment 6

⁹⁰ Revised per Amendment 6

⁹¹ Paragraph revised per Amendments 5, 6 and 8

Assuming approximately 30% of patients will not be eligible for the primary efficacy analysis (ie, will not have a pre-therapy Gram-negative organism) a total of 362 ITT patients per group (724 ITT overall) will be needed for the study, based on current surveillance. Note that with this sample size, an observed treatment group difference of as low as 7.74% could provide a statistically significant result.

11.3 Methods for the Analysis of the Primary Efficacy Parameter (Survival) - amended

⁹²The primary efficacy variable is Survival through the LFU visit. Survival is achieved when the patient is alive through the LFU visit. No other factors are considered in the evaluation of survival.

The primary analysis will compare the survival rates through LFU visit of patients in the BAY 41-6551 group versus patients in the placebo group, using the combined data from studies 13084 and 13085.

The null (H_0) and the alternative (H_1) hypothesis for this primary analysis is the following:

- $H_0: p[\text{BAY 41-6551}] = p[\text{placebo}]$
- $H_1: p[\text{BAY 41-6551}] \neq p[\text{placebo}]$

where p is the true Survival rate.

A Cochran-Mantel-Haenzel test of general association, adjusting for stratum and geographic region, will be performed as the primary efficacy analysis. If the p -value from this test is less than 0.05, and the proportion of patients who survive is higher in the BAY 41-6551 group than in the placebo group, the study will have achieved its primary objective.

In addition, as a supportive analysis, a 95% confidence interval will be calculated for the odds ratio. This confidence interval will be generated from a logistic regression model with Survival as the primary variable, and treatment, stratum, and geographic region as the independent variables. If the lower limit of the 95% confidence interval for the odds ratio (BAY 41-6551/placebo) is greater than 1, BAY 41-6551 will be demonstrated to be statistically superior to placebo.

Tests will be performed using the SAS procedure FREQ, and the 95% confidence intervals for the odds ratios will be generated using PROC LOGISTIC.

An unadjusted chi-squared test will also be performed as a supportive efficacy analysis. In addition, a logistic regression model with only treatment as an independent variable will be performed, and the resulting 95% confidence interval for the odds ratio will be provided. These analyses will serve as sensitivity analyses to demonstrate consistency with the primary analysis.

The Breslow-Day test will be used as a further supportive analysis to test for treatment by geographic region and treatment by stratum interaction. If this test of the homogeneity of the

⁹² Section revised per Amendment 6 and 8

odds ratio indicates a significant interaction, exploratory analyses will attempt to define its source. A Cochran-Mantel-Haenzel test of general association, adjusting for stratum and study protocol (ie, 13084 or 13085), will be performed to assess the effect of study protocol on the primary efficacy variable Survival. Geographic region will not be included in this model as the 2 studies were conducted in different regions.

The primary efficacy analysis performed on the mITT population will be repeated for ITT population.

Exploratory descriptive summaries will be provided for the primary efficacy variable by treatment group and pre-determined subgroups of interest. These subgroups will include:

- Type of ventilator
- Underlying diagnosis
- Positive or negative blood culture
- CPIS at pre-therapy (< 6, 6, 7, 8, 9, 10, 11)
- APACHE II score (< 20, \geq 20)
- Age (<18, 18 to <45, 45 to < 65, 65 to <75, \geq 75 years)
- Sex
- Race
- Country
- Geographic region
- Latin America countries (Brazil, Colombia, Mexico)
- Asia Pacific countries (Philippines, South Korea, Taiwan, Thailand, China, Japan)
- Baseline Gram-negative antibiotic treatment taken by each patient (1, 2, \geq 3)
- Primary reason for intubation (Current pneumonia-related respiratory failure vs everything else)
- Patients who received IV antibiotic for pneumonia \geq 5 days after day of first intubation (Yes, No);
- Patients who received at least one dose of carbapenem during Days 1 through 10 (Yes, No);
- Start time of amikacin from start time of IV antibiotic (0 to <12 hours, 12 to <24 hours, \geq 24 hours).
- Patients with confirmed MDR pathogens (MDR first detected at baseline, MDR first detected post-baseline, Not MDR);
- Patients with confirmed ESBL pathogens (ESBL first detected at baseline, ESBL first detected post-baseline, Not ESBL);

The last 2 subgroups above pertain to MDR designation which is described in detail in Appendix 9.1:

- To be declared a MDR, a bacterial isolate at the same visit must be resistant using the central laboratory interpretation to at least 3 of the 7 drug classes on the susceptibility panel: aminoglycoside, β -lactam/ β -lactamase inhibitor, cepham, carbapenam, tetracycline, folate pathway inhibitor, and quinolone. Once a patient has any MDR pathogen, he/she should be designated as a MDR patient no matter what the subsequent susceptibility tests show.
- For the 3 cepham (ceftazidime, cefazolin, and cefpodoxime), resistance to any one of the 3 drugs in the panel counts as cepham resistance for the category.
- An interpretation by central laboratory of “Not applicable” result will be considered as “susceptible” for purposes of MDR tabulation. This means that at least 3 results of “intermediate” or “resistant” are necessary for an MDR designation, and a “Not applicable” will not be included in the total.

11.4 Methods for the Analysis of Secondary Efficacy Parameters - amended

⁹³ If the null hypothesis for the primary efficacy variable is rejected, a formal hypothesis testing scenario will be applied for the secondary efficacy variables:

- Pneumonia-related mortality through the LFU visit (determined by blinded adjudication committee)
- Early Clinical Response (based on CPIS, mortality, and certain AEs) assessed through Day 10
- The number of days on mechanical ventilation through the LFU visit
- The number of days in the ICU through the LFU visit

The secondary efficacy variables will be formally tested for statistical significance of a difference between the BAY 41-6551 group versus the placebo group, only if the primary efficacy comparison is statistically significant at the two-sided 5% level. A sequential testing procedure will be performed at the two-sided alpha level of 0.05 for these four secondary efficacy variables, strictly in the order listed above.

The null hypothesis of no difference between BAY 41-6551 and placebo in pneumonia – related mortality and early clinical response will be tested using an unadjusted Chi-square test. Analysis of variance will be used to test the null hypothesis of no difference between BAY 41-6551 and placebo for the number of days on mechanical ventilation and in the ICU.

For the purpose of the sequential testing procedure, the only effect in the models will be treatment. As supportive analyses, additional models will be used with effects included for

⁹³ Section revised per Amendments 5 and 6

geographic region for all secondary variables. Non-parametric tests for treatment comparisons will be considered as sensitivity analyses.

The secondary endpoint of pneumonia-related mortality through the LFU visit will be examined further by subgroups listed for the primary analysis.

All 4 secondary endpoints will be examined further by the following MDR subgroups:

- Patients with confirmed MDR pathogens (MDR first detected at baseline, MDR first detected post-baseline, Not MDR);
- Patients with confirmed ESBL pathogens (ESBL first detected at baseline, ESBL first detected post-baseline, Not ESBL);
- Patients who received IV antibiotic for pneumonia ≥ 5 days after day of first intubation (Yes, No);
- Patients who received at least one dose of carbapenem during Day 1 through 10 (Yes, No);
- Start time of amikacin from start time of IV antibiotic (0 to <12 hours, 12 to <24 hours, ≥ 24 hours).

⁹⁴The other efficacy endpoints are:

1. The number of days in the hospital through LFU visit
2. Relapse rates at LFU
3. Total number of days of Gram-negative antibiotics
4. Change in component of CPIS score from baseline to TOC
5. Clinical response rates at EOT (Clinical cure, Clinical failure)

Analysis of variance will be used to test the null hypothesis of no difference between BAY 41-6551 and placebo for the total number of days of Gram-negative antibiotics. The other four efficacy endpoints listed above will be summarized descriptively.

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11.5 Additional Analyses of Clinical Success - amended

⁹⁵ The following endpoints will be analyzed as additional analyses of clinical success:

11.5.1 Foundation for the National Institute of Health Criteria - amended

Clinical success using FNIH recommendations is defined as mITT patients who survived through the LFU visit and did not have septic shock. Patients will be designated as having a

⁹⁴ Revised with Amendment 8

⁹⁵ Section added per Amendment 8

septic shock event based on the standard medical queries (SMQ) terms tabulated as adverse events. Descriptive analysis will be provided with 95% confidence intervals. Cochran-Mantel-Haenszel test of general association adjusting for stratum and geographic region will also be performed.

11.5.2 Investigator Assessment of Patient Outcome - amended

Investigator Assessment of Patient Outcome is determined at the TOC visit. The outcomes of “success” or “failure” are based on the following criteria:

- Improvement or lack of progression of all abnormalities on chest radiograph
- Resolution towards normal of the following CPIS components: tracheal secretions (volume and purulence), temperature, blood leukocytes, oxygenation (P/F ratio)
- Any further change to the Gram-negative portion of the antimicrobial regimen being used to treat pneumonia during the first 10 days, after the initial antimicrobial adjustment within the first 96 hours after the initiation of empiric therapy or as soon as initial culture and susceptibility results are available and excepting the discontinuation of aminoglycosides after 5-7 days, would be considered a Clinical Failure
- Patient did not receive antibiotic therapy for pneumonia after Day 10 (EOT)
- Patient survived through the TOC visit

All 5 conditions listed above must be met to achieve Investigator’s Assessment of Patient Outcome to be a Success. At the LFU visit, an assessment of relapse will be considered to be Failure.

These endpoints will be summarized descriptively with 95% confidence interval. A Cochran-Mantel-Haenszel test of general association adjusting for stratum and geographic region will be performed on the mITT patients.

In addition, Kaplan-Meier curves will be provided for time to Investigator Assessment of Clinical Failure. Time to Clinical Failure is defined as the time from the first day of study drug intake to the first time at which clinical failure is assessed. Patients who do not fail will be censored at death date, their LFU visit or last visit.

11.5.3 Clinical Success (Former 5 Component Primary Endpoint) - amended

Clinical Success is achieved when the following criteria are met as listed in the order of medical relevance:

- The patient must survive through the Late Follow-Up (LFU) visit
- Systemic antibiotics (IV or PO) for pneumonia must be stopped on or before the TOC visit (Day 17-19),
- Systemic antibiotics (IV or PO) for pneumonia must not be restarted after the TOC visit through the LFU visit
- The patient must have stable respiratory function evaluated at TOC or last visit based on the PaO₂/FiO₂ (P/F) ratio as outlined below (if P/F ratio is not available at the TOC, use the P/F ratio value from the closest previous visit), and

- The patient must not have a reported AE of lung abscess or empyema through the LFU visit

Stable respiratory function

- Patient is extubated at the TOC visit or
- Patient is intubated at the TOC and:
 - Patient has P/F ratio > 200 at the TOC visit or
 - Patient has P/F ratio > 100 and ≤ 200 at the TOC visit and:
 - Patient had a P/F ratio ≤ 200 at baseline

If ventilation status not explicitly known to be extubated for a patient at TOC or last visit, the status was assumed to be intubated for the determination of primary endpoint.

Unstable respiratory function

- Patient has a P/F ratio ≤ 100 at the TOC visit or
- Patient has a P/F ratio > 100 and ≤ 200 at the TOC visit and:
- Patient has P/F ratio > 200 at baseline

The outcome is Clinical Success if all 5 criteria are met. If any one of the criteria is not met, then the patient is considered a Clinical Failure. Patients who do not have a clinical assessment of success due to missing data will be considered a Clinical Failure.

For patients who discontinue study drug (on vent or handheld) for reasons other than efficacy will be handled as described in the table below:

Reason for Discontinuation of Aerosol Therapy	Outcome / Comments
No Gram-negative bacteria isolated from a pre-therapy respiratory specimen	Patient is considered ITT analysis and not evaluated for efficacy analysis as mITT
Patient withdrew consent or refused handheld device	Evaluate for efficacy if all data for primary efficacy are available; if data are missing, then failure
Death	Failure
Adverse event	Failure
New therapy incompatible with aerosol therapy	Failure
Lost to follow-up	Failure
Any other reason/unknown reason	Failure

Additional reasons for discontinuation may be included as failure after review of blinded data. The patient must have stable respiratory function evaluated at TOC or last visit based on the ventilation status and PaO₂/FiO₂ (P/F) ratio (if ventilation status or P/F ratio is not available at the TOC, use the respective ventilation status or P/F ratio value from the closest previous visit). See Section **Error! Reference source not found.**, Definition of Primary Efficacy Endpoint.

The analysis will compare the proportion of patients with Clinical Success in the BAY 41-6551 group versus the patients in the placebo group, using the combined data from studies 13084 and 13085. All assessments other than Clinical Success, which are failures, improvements, and missing (those patients who do not have a TOC assessment) will be grouped together in the Clinical Failure category for the purpose of this analysis. If a TOC assessment date is missing for determining the antibiotic criteria for a patient, the TOC assessment will be assumed to have occurred 17 days after the start of study drug.

A Cochran-Mantel-Haenszel test of general association, adjusting for stratum and geographic region, will be performed as the primary efficacy analysis. If the p-value from this test is less than 0.05, and the proportion of patients with Clinical Success is higher in the BAY 41-6551 group than in the placebo group, the study will have demonstrated superiority in this sensitivity analysis.

In addition, as a supportive analysis, a 95% confidence interval will be calculated for the odds ratio. This confidence interval will be generated from a logistic regression model with Clinical Success as the additional efficacy variable, and treatment, stratum, and geographic region as the independent variables. If the lower limit of the 95% confidence interval for the odds ratio (BAY 41-6551/placebo) is greater than 1, BAY 41-6551 will be demonstrated to be statistically superior to placebo.

Individual components of the composite endpoint will be analyzed using the Cochran-Mantel-Haenszel test adjusting for stratum and geographic region. This is to assess the components are moving in the same general direction and which, if any, single component is driving the result. The analysis of individual components will be performed on the actual counts of each criterion, not ordered by medical relevance.

Tests will be performed using the SAS procedure FREQ, and the 95% confidence intervals for the odds ratios will be generated using PROC LOGISTIC.

An unadjusted chi-squared test will also be performed as a supportive efficacy analysis. In addition, a logistic regression model with only treatment as an independent variable will be performed, and the resulting 95% confidence interval for the odds ratio will be provided.

The Breslow-Day test will be used as a further supportive analysis to test for treatment by geographic region and treatment by stratum interaction. If this test of the homogeneity of the odds ratio indicate significant interaction ($P < 0.10$), exploratory analyses will attempt to define its source.

A Cochran-Mantel-Haenszel test of general association, adjusting for stratum and study protocol (i.e., 13084 or 13085), will be performed to assess the effect of study protocol on the Clinical Success as additional efficacy variable. Geographic region will not be included in this model as the 2 studies were conducted in different regions.

Number and percent of patients meeting the each failure criteria will be summarized in the order of medical relevance as presented in Section 6.2.2. A patient with failure is counted only in the criteria with highest medical relevance in the order presented. Patients may not have any failure criteria, but not be included in the analysis due to missing data. To account for missing visits, the number of patients without failure criteria but has TOC visit and missing LFU visit will be presented. Additional summary of respiratory stability function will be given for components of stable respiratory function and unstable respiratory function for each treatment group.

11.6 Analysis of Device Performance

Device performance will be summarized descriptively as reported events, incidents, complaints and analysis of planned return units. No inferential statistics will be provided.

11.7 Analysis of Safety Data

All analyses of safety endpoints will be descriptive only, and no inferential statistics will be provided.

The proportion of patients with organ failure will be summarized by treatment group. The overall proportion of patients with any organ failure will be summarized, as well as the proportion of patients with each specific type of organ failure.

The incidence rates of treatment-emergent AEs, drug-related and device-related AEs, SAEs, drug-related and device-related SAEs, and premature discontinuations due to AEs will be presented by treatment group, MedDRA preferred term, and system organ class.

Mortality rates will be summarized during therapy, and at Day 15 and Day 28 by treatment group. Ninety-five percent confidence intervals will also be provided for the difference between groups in mortality rates at these time points. In addition, Kaplan-Meier curves will be provided for time to death.

Descriptive statistics for actual values and change from baseline values for clinical laboratory tests will be presented. Incidence rates of treatment-emergent abnormally high or low clinical laboratory tests will also be provided.

11.8 Methods for the Analysis of the Microbiology Endpoints

Summaries of microbiologic endpoints will only be provided for the mITT population.

By-patient and by-organism bacteriological eradication rates at the TOC visit will be provided for each treatment group. In these summaries, eradication rates will be defined as the sum of eradications and presumed eradications divided by the sum of eradications, presumed eradications, persistence, presumed persistence, and indeterminate.

Rates of emergent infections (new infections and superinfections) will be summarized separately, by treatment group. By-patient and by-organism displays will be provided for each treatment group for each type of emergent infection.

12. Adverse Events

12.1 Definitions

12.1.1 Adverse Event

An AE is any untoward undesirable experience associated with the use of a medicinal product or medical device in a patient. The AE does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the medicinal product.

Adverse events associated with the use of a drug in humans, whether or not considered drug related, include the following:

- An AE occurring in the course of the use of a drug product in professional practice.
- An AE occurring from an overdose whether accidental or intentional.
- An AE occurring from drug abuse.
- An AE occurring from drug withdrawal.
- An AE where there is a reasonable possibility that the event occurred purely as a result of the patient's participation in the study (eg, AE or SAE due to discontinuation of anti-hypertensive drugs during wash-out phase) must also be reported as an AE even if it is not related to the investigational product.

The clinical manifestation of any failure of expected pharmacological action is not recorded as an AE if it is already reflected as a data point captured in the CRF. If, however, the event fulfills any of the criteria for an SAE, it must be recorded and reported as such.

12.1.2 Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is a medically important event as judged by the investigator.

Life-threatening: The term “life-threatening” in the definition of “serious” refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an AE which hypothetically might have caused death if it were more severe.

Hospitalization: Any AE leading to hospitalization or prolongation of hospitalization will be considered as serious, UNLESS at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours and is not otherwise associated with a medically important AE.
OR
- The admission is pre-planned (ie, elective or scheduled surgery arranged prior to the start of the study).
OR
- The admission is not associated with an AE (eg, social hospitalization for purposes of respite care).

However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of ‘medically important’ and as such may be reportable as a serious AE dependent on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Disability means a substantial disruption of a person’s ability to conduct normal life’s functions.

Important medical event: Any AE may be considered serious because it may jeopardize the patient and may require intervention to prevent another serious condition. As guidance for determination of important medical events refer to the Eudravigilance Important Medical Event (IME) Terms List. These terms either refer to or might be indicative of a serious disease state.

Such reported events warrant special attention because of their possible association with a serious disease state and may lead to more decisive action than reports on other terms.

12.1.3 Unexpected Adverse Event

An unexpected AE is any adverse drug event, the specificity or severity of which is not consistent with the current Investigator Brochure (or Package Insert for marketed products). Also, reports which add significant information on specificity or severity of a known, already documented AE constitute unexpected AEs. For example, an event more specific or more severe than described in the Investigator Brochure would be considered “unexpected”. Specific examples would be; (a) acute renal failure as a labeled AE with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

The expectedness of AEs, including the expectedness of AEs related to the medical device, will be determined by the sponsor according to the applicable reference document and according to all local regulations.

12.1.4 Adverse Events of Special Safety Interest

Identified risks of parenteral (IV and IM) formulations of amikacin (eg, neurotoxicity, ototoxicity, and nephrotoxicity) should be monitored to assess the potential risk for aerosolized amikacin. Adverse effects due to local exposure in the bronchopulmonary system, such as bronchospasm (see Section 8.4.6.2), coughing during or shortly after inhalation of aerosol, and hemoptysis should also be monitored.

12.1.5 Relationship of Adverse Event to Investigational Product

The assessment of the relationship of an AE to the administration of study drug is a clinical decision based on all available information at the time of the completion of the CRF.

An assessment of ‘No’ would include:

1. The existence of a clear alternative explanation eg, mechanical bleeding at surgical site.

OR

2. Non-Plausibility eg, the patient is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of ‘Yes’ indicates that there is a reasonable suspicion that the AE is associated with the use of the investigational drug.

Factors to be considered in assessing the relationship of the AE to study drug include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on discontinuation (de-challenge), recurrence on reintroduction (re-challenge): Patient’s response after drug discontinuation (de-challenge) or patient’s response after drug re-introduction (re-challenge) should be considered in the view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant medication or treatment: The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them may be suspected to cause the event in question.
- The pharmacology and pharmacokinetics of the test drug: The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the test drug(s), coupled with the individual patient’s pharmacodynamics should be considered.

12.1.6 Severity of the Adverse Event

The following classification should be used:

The severity of AEs should be graded as follows:

Mild – usually transient in nature and generally not interfering with normal activities

Moderate – sufficiently discomforting to interfere with normal activities

Severe – prevents normal activities

12.1.7 Adverse Event Documentation

All AEs occurring after the patient has signed the informed consent until the completion of the end of study visit must be fully recorded in the patient's CRF and transcribed to the electronic CRF (eCRF).

Documentation must be supported by an entry in the patient's file. A laboratory test abnormality considered clinically relevant, eg, causing the patient to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an AE. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

12.2 Reporting of Serious Adverse Events/Pregnancy

All investigators will be trained on all relevant aspects of the investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

Serious AEs, including laboratory test abnormalities fulfilling the definition of serious, after signing the informed consent and during follow-up period must immediately (within 24 hours of the investigator's awareness) be reported to the person detailed in the study file. An SAE form must also be completed within 24 hours of the investigator awareness and forwarded to the designated person as detailed in the study file. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated person.

When required, and according to local law and regulations, SAEs must be reported to the Ethics Committee and Regulatory Authorities.

Pregnancy occurring during a clinical investigation, although not considered an SAE, must be reported to Bayer within the same timelines as an SAE on a Pregnancy Monitoring Form. The outcome of a pregnancy should be followed up carefully and any abnormal outcome of the mother or the child should be reported. This also applies to pregnancies following the administration of the investigational product to the father prior to sexual intercourse. Bayer usually does not gather information of drug exposure of the father, however, if those cases are reported, all efforts should be made to obtain similar information on course and outcome, subject to the partner's consent.

12.2.1 Notification of the IECs/IRBs

Notification of the IECs/IRBs about all relevant events (eg, SAEs, SUSARs) will be performed by the sponsor or delegated to a CRO and/or by the investigator according to all applicable regulations.

12.2.2 Notification of the Authorities

The processing and reporting of all relevant events (eg, SAEs, SUSARs) to the authorities will be done by the sponsor according to all applicable regulations.

12.2.3 Sponsor's Notification of the Investigational Site

The sponsor or sponsor's designee will inform all investigational sites about reported relevant events (eg, SUSARs) according to all applicable regulations.

12.3 Definition of an Incident

An incident is any malfunction or deterioration in the characteristics and/or performance of the device, as well as any inadequacy in the labeling or the instructions for use, which directly or indirectly, might lead to or might have led to the death or to a serious deterioration in the state of health of a patient or user or of other persons.

The following criteria apply in determining whether an incident has occurred:

- A. An event has occurred or may occur if the same failure is repeated.

An event could be among others:

- Malfunction or deterioration in the characteristics or performance or
- Unanticipated adverse reaction or unanticipated side effect or
- Interactions with other substances or products or
- Degradation / destruction of the device (e.g., fire) or
- Inappropriate therapy, or
- Inaccuracy in the labeling, instructions for use including omissions or deficiencies.

- B. The device is suspected to be a contributory cause of the event

- C. The event led, or might have led, to one of the following outcomes:

- Death of a patient or user or other person or
- Serious deterioration in the state of health of a patient, user or other person

To determine whether an incident has occurred, criteria A, B, and C must be fulfilled. All incidents will be reported to the respective national competent authorities, authorized representative, and as applicable, notified bodies according to local regulations and medical device regulations 93/42/EEC, MEDDEV 12.2, GHTF/SG2/N21R8:1999, and 21 Code of Federal Regulations (CFR) Part 803.

Incidents should be reported using a separate clinical investigations device complaint form.

12.3.1 Device Malfunction or Failure and Medical Device Reporting

Any device complaint, malfunction, or failure including use errors will be recorded by the clinical/investigational site, including all relevant device information using the clinical investigations device complaint form, and forwarded within 24 hours to the sponsor or sponsor's designee for evaluation and investigation, regardless of whether or not a medical

event was associated with the device malfunction or failure. There are three different situations, in which a medical device complaint form might need to be filled out by the investigator:

- a) When an AE is recorded, the investigator needs to check if a device malfunction or failure might be associated with the recorded AE.
- b) When a device malfunction or device failure occurs, the investigator needs to assess whether an AE might have occurred in relation to the device.
- c) When a device malfunction, device failure, or use error occurs, without any associated AE, this also needs to be captured in the form and immediately forwarded to the sponsor for investigation.

The details of the malfunction and medical circumstances will be captured on a Device Complaint Form filled out by the investigator and then returned to the sponsor or sponsor's designee. The final determination of reportability is made by the sponsor and not the clinical/investigational site based on the medical circumstances surrounding the event. Novartis, the device manufacturer, may recommend reporting an incident based on investigations, but the final determination of reportability is made by the sponsor.

Investigator's notification of the sponsor

All investigators will be instructed and trained on all relevant aspects of the investigator's reporting obligations for device incidents and serious public health threats. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

The sponsor will inform the device manufacturer (Novartis) about any incident and Novartis will then perform an evaluation and investigation of the device, as necessary, and exchange any significant information with the sponsor. Novartis will inform the sponsor about necessary trend reports and will provide the required documentation after completing the respective investigation and statistical analysis. The sponsor will then notify the authorities of any trend reports according to all applicable regulations.

All devices that have malfunctioned or failed will be inventoried and returned to the device manufacturer. The devices should be stored in a hermetically sealed bag and labeled with the respective case reference. In cases where an incident is recorded in connection with the device malfunction or failure, the device should be sent immediately per courier to the device manufacturer. If any of the devices need to be replaced, the reason(s) will be documented. Additional PDDS Clinical devices are provided for this purpose.

13. Use of Data and Publication

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor, who may utilize the data in various ways, such as for submission to government regulatory authorities or disclosure to other investigators. The investigator, while free to utilize data derived from the study for scientific purposes, must discuss any publication with the sponsor prior to release and obtain written consent of the sponsor on the intended publication. The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator must send a draft

manuscript of the publication or abstract to the sponsor thirty days in advance of submission in order to obtain approval prior to submission of the final version for publication. This will be reviewed promptly and approval will not be withheld unreasonably. In case of a difference of opinion between the sponsor and the investigator(s), the contents of the publication will be discussed in order to find a solution which satisfies both parties.

14. References - amended

1. Schaad UB, Wedgewood-Krucko J, Suter S, et al. Efficacy of inhaled amikacin as an adjunct to intravenous combination therapy (ceftazidime and amikacin) in cystic fibrosis. *J Pediatr* 1987;111(4):599-605.
2. Dequin P-F, Faurisson F, Lemarie E, et al. Urinary excretion reflects lung deposition of aminoglycoside aerosols in cystic fibrosis. *Eur Resp J* 2001;18:316-22.
3. Palmer LB, Smaldone GC, Simon SR, et al. Aerosolized antibiotics in mechanically-ventilated patients: delivery and response. *Crit Care Med* 1998;26:31-9.
4. Qanta A, Ahmed A, Niederman MS. Respiratory infection in the chronically critically ill patient. *Clin Chest Med* 2001;22(1):71-85.
5. American Thoracic Society and the 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.
6. American Thoracic Society. Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy, and preventative strategies: A Consensus Statement. *Am J Respir Crit Care Med* 1995;153:1711-25.
7. Chastre, J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2002;165:867-903.
8. Micek ST, Ward S, Fraser VJ, et al. A randomized controlled study of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia. *Chest* 2004;125(5):1791-9.
9. Heyland DK, Cook DJ, Griffith L, et al. Canadian Critical Trials Group. The attributable morbidity and mortality of ventilator-associated pneumonia in the critically ill patient. *Am J Resp Crit Care Med* 1999;159:1249-56.
10. Richards M, Edwards JR, Culver DH, et al. The national nosocomial infections surveillance system. Nosocomial infections in medical intensive care units in the United States. *Crit Care Med* 1999;27(5):887-92.
11. Dennesen P, van der Ven A, Kessels A, et al. Resolution of infectious parameters after antimicrobial therapy in patients with ventilator-associated pneumonia. *Am J Resp Crit Care Med* 2001;163:1371-5.
12. Singh N, Rogers P, Atwood C, et al. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. *Am J Resp Crit Care Med* 2000;162:505-11.
13. Chastre J, Wolff M, Fagon, J, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults. *JAMA* 2003;290:2588-98.

14. Santré C, Georges H, Jacquier JM, et al. Amikacin levels in bronchial secretions of 10 pneumonia patients with respiratory support treated once daily versus twice daily. *Antimicrob Agents Chemother* 1995;39(1):264-7.
15. MacLusky IB, Gold R, Corey M, et al. Long-term effects of inhaled tobramycin in patients with cystic fibrosis colonized with pseudomonas aeruginosa. *Pediatr Pulmonol* 1989;7(1):42-8.
16. Smith AL, Ramsey BW, Hedges DL, et al. Safety of aerosol tobramycin administration for 3 months to patients with cystic fibrosis. *Pediatr Pulmonol* 1989;7(4):256-71.
17. Fink JB, Dhand R. Aerosol therapy in mechanically-ventilated patients: recent advances and new techniques. *Semin Resp Critical Care Med* 2000;21(3):183-201.
18. Smaldone GC, Palmer LB. Aerosolized antibiotics: current and future. *Respir Care* 2000;45(6):667-75.
19. Duarte AG, Fink JB. Inhalation therapy during mechanical ventilation. *Resp Care Clin N Am* 2001;7(2):233-60.
20. Langer M, Mosconi P, Cigada M, et al. Long-term respiratory support and risk of pneumonia in critically ill patients. *Am Rev Respir Dis* 1989;140(2):302-5.
21. Cook DJ, Walter SD, Cook RJ, et al. Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. *Ann Intern Med* 1998;129(6):433-40.
22. Rello J, Torres A. Microbial causes of ventilator-associated pneumonia. *Semin Respir Infect* 1996;11(1):24-31.
23. Luna CM, Vujacich P, Niederman MS, et al. Impact of BAL data on the therapy and outcome of ventilator-associated pneumonia. *Chest* 1997;111(3):676-85.
24. Rello J, Diaz E. Pneumonia in the intensive care unit. *Crit Care Med* 2003;31(10):2544-51
25. Goldstein I, Wallet F, Nicolas-Robin A, et al. Lung deposition and efficiency of nebulized amikacin during Escherichia coli pneumonia in ventilated piglets. *Am J Resp Crit Care Med* 2002;166:1375-81.
26. Ferrari F, Goldstein I, Nieszkowszka A, et al. Lack of lung tissue and systemic accumulation after consecutive daily aerosols of amikacin in ventilated piglets with healthy lungs. *Anesth* 2003;98(4):1016-9.
27. Wood GC, Boucher BA. Aerosolized antimicrobial therapy in acutely ill patients. *Pharmacotherapy* 2000;20(2):166-81.
28. Lipworth BJ. Pharmacokinetics of inhaled drugs. *Br J Clin Pharmacol* 1996;42(6):697-705.
29. Kondili E, Georgopoulos D. Aerosol medications. *Respir Care Clin N Am* 2002;8(2):309-34.

30. Dhand R. Basic techniques for aerosol delivery during mechanical ventilation. *Respir Care* 2004;49(6):611-22.
31. Odio W, Van Laer E, Klastersky J. Concentrations of gentamicin in bronchial secretions after intramuscular and endotracheal administration. *J Clin Pharmacol* 1975;15(7):518-24.
32. Dally MB, Kurrle S, Breslin AB. Ventilatory effects of aerosol gentamicin. *Thorax* 1978;33(1):54-6.
33. Prober CG, Walson PD, Jones J. The Committee on Infectious Diseases and Committee on Drugs. Technical report: precautions regarding the use of aerosolized antibiotics. *Pediatrics* 2000;106(6):1-6.
34. Flores RM, Starke B, Kramer T, et al. Aerosolized antibiotics and microbial resistance in mechanically ventilated patients [abstract]. 2001 Meeting of the American Thoracic Society; 2001; San Francisco, California.
35. Sorensen VJ, Horst HM, Obeid FN, et al. Endotracheal aminoglycosides in Gram-negative pneumonia. *Am Surg* 1986;52(7):391-4.
36. Faurisson F, Delatour F, Jelazko P. A simple tool for monitoring nebulized amikacin treatments based on a single urine assay. *J Aerosol Med* 2001;14(1):73-81.
37. Lancon JP, Caillard B, Manuelian M, et al. Lung and serum amikacin concentrations after a single endotracheal dose in man. *Ann Fr Anesth Reanim* 1991;10(3):230-4.
38. Faurisson F, Gherzi B, Chazalotte JP. Pharmacokinetics of aerosolized amikacin in cystic fibrosis. *Am Rev Respir Dis* 1991;A294.
39. Faurisson F, Delatour F, Helyne D, et al. Respiratory monitoring of inhalation increases the deposition of aerosolized amikacin (AMK) in healthy volunteers. Poster, 33rd Interscience Conf on Antimicrobial Agents & Chemotherapy 1993.
40. Standridge JB, Aliff CL. Aerosolized amikacin in the treatment of pseudomonas pneumonia in the nursing home setting. *South Med J* 2001;94(2):244-6.
41. Investigator's Brochure, Amikacin Pulmonary Delivery System; Version 4.0: 19 FEB 2015. ⁹⁶
42. Morris A, Tanner D, Reller L. Rejection criteria for endotracheal aspirates from adults. *Journal of Clinical Microbiology* May 1993;31:1027-9.
43. Wood GC, Hanes SD. Comparison of ampicillin-sulbactam and imipenem-cilastatin for the treatment of acinetobacter ventilator-associated pneumonia. *Clinical Infectious Disease* 2002;34:1425-30.
44. Garnacho-Montero J. et al. Treatment of multidrug-resistant acinetobacter baumannii ventilator-associated pneumonia (VAP) with intravenous colistin: A comparison with imipenem-susceptible VAP. *Clinical Infectious Disease* 2003; 36:1111-8.

⁹⁶ Updated per Amendment 16.

45. Luna CM, et al. Resolution of ventilator-associated pneumonia: prospective evaluation of the clinical pulmonary infection score as an early clinical predictor of outcome. *Crit Care Med* 2003;31(3):676-82.
46. Knaus WA, et al. APACHE II: A severity of disease classification system. *Crit Care Med* 1985;13(10):818-29.
47. Anon. Endotracheal suctioning of mechanically ventilated patients with artificial airways 2010. *Respir Care* 2010 Jun;55(6):758-64.
48. Kelman GR. Digital computer subroutine for the conversion of oxygen tension into saturation. *J Appl Physiol* 1966 Jul;21(4):1375-6.

15. Appendices

15.1 Study Flow Chart and Schedule of Procedures - Amended

Assessment	Screening	Day										Premature D/C/Early Withdrawal	TOC Day 17 to 19	Late Follow-Up Day 28 to 32 ^b	
		1	2	3	4	5	6	7	8	9	10 ^a EOT			In Person	By Phone
		Informed Consent	X												
Inclusion/Exclusion Criteria	X														
Medical/Surgical/Medication Hx	X														
Concomitant Medication ^c	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Exam/Vitals ^d	X											X	X	X	
Brief Physical Exam/Vitals ^e		X	X	X	X	X	X	X	X	X	X				
Assessment of clinical signs & symptoms of pneumonia	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chest X-Ray	X	X		X		X		X			X	X	X	X ^r	
Urine or Serum pregnancy test ^f	X														
Hematology/Serum Chemistry/Urinalysis	X	X		X		X		X			X	X	X	X	
Serum creatinine ^g		X	X	X	X	X	X	X	X	X	X				
Aerobic blood culture ^h	X														
Arterial blood gases/pulse oximetry ⁹⁷	X	X		X		X		X			X	X ^s	X ^s	X ^r	
Collection of ventilator parameters pre- and post-dose ⁹⁸		X	X	X	X	X	X	X	X	X	X ⁹⁹				
Collect respiratory specimen for Gram stain and culture ⁱ	X	X		X		X		X			X	X	X	X ^r	
Pleural fluid culture ^j	X														

⁹⁷ Footnote s added with Amendment 6.

⁹⁸ Per Amendment 5

⁹⁹ Added with Amendment 6 as it was erroneously omitted.

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CPIS ^k	X	X		X		X			X			X	X	X	
APACHE II score	X														
Randomization		X													
Dispense PDDS Clinical Device		X ^m													
Dispense Study Medication/Nebulizer		X ⁿ	X	X	X	X	X	X	X	X	X				
Administer Study Medication		X ^o	X	X	X	X	X	X	X	X	X				
Serum amikacin trough level ^p		X	X	X	X	X	X	X	X	X	X				
AEs	X ^q	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adjunct Therapy and Procedures		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Investigator Assessment of Patient Outcome ¹⁰⁰											X	X	X	X	X
Late Follow-Up Questionnaire														X	X

Notes: Screening is within 48 hours prior to randomization. AEs = adverse events; APACHE II = Acute Physiology and Chronic Health Evaluation II; BAL = bronchoalveolar lavage; CPIS = Clinical Pulmonary Infection Score; D/C = discontinuation; EOT = end of therapy; Hx = history; LFU = late follow-up; PBS = protected specimen brush; TA = tracheal aspirate; TOC = Test-of-Cure.

a - All assessments at Day 10 should be done after the last dose of aerosolized treatment that corresponds to the completion of 20 doses

b - Patients will be strongly encouraged to return to their study facility for their LFU. This questionnaire needs to be completed whether in person or via a phone conversation with the patient, or the patient's advocate including recording concomitant medication and AEs.

c - Include previous concomitant or post-therapy antibacterials, antifungals, and antivirals (within two weeks before start of treatment or during follow-up)

d - Include weight, height (screening visit only), heart rate, blood pressure, respiratory rate, daily maximum temperature, and complete review of body systems

e - Include weight, heart rate, blood pressure, respiratory rate, daily maximum temperature, and review of body systems

f - Females of child-bearing potential only

g - Serum creatinine levels should be obtained once daily and the results available and reviewed prior to the next dose

h - Culture should be obtained from two separate venipuncture sites. If the result is positive, repeat as needed (Days 1, 3, 5, 7, 10, TOC, LFU) until negative.

i - A respiratory specimen (eg, TA, BAL, mini-BAL, or PSB) will be obtained for Gram stain, semi-quantitative or quantitative culture, and susceptibility testing. **NOTE:** All respiratory specimens will be evaluated by Gram stain and rejected for culture if the Gram stain reveals >10 squamous epithelial cells per low powered (100 x) field.

j - Pleural fluid cultures should only be obtained for patients with evidence of a pleural effusion and if clinically indicated. Cultures from any other respiratory specimens should also be obtained if clinically indicated. If the result is positive, repeat as needed if clinically indicated (Days 1, 3, 5, 7,10, TOC, LFU) until negative.

k - CPIS must be greater than or equal to 6 for inclusion into study.

¹⁰⁰ As per Amendment 6

l – Footnote deleted per Amendment 6.

m - Prior to the first dose, each patient will receive a unique PDDS Clinical device consisting of a unique control module, T-piece adaptor, AC/DC adaptor, air pressure feedback device, and cable.

n - Prior to each dose, each patient will receive a one vial of study medication (either BAY 41-6551 or placebo) and one nebulizer/reservoir.¹⁰¹

o - Patients will be started on aerosolized study medication within 48 hours of systemic antibiotic therapy being initiated. Patients will receive 3.2 mL of either BAY 41-6551 (400 mg, amikacin as free base) or placebo every 12 hours via the PDDS Clinical for ten days (20 doses). If a patient is extubated during the course of treatment or has had a tracheostomy and is spontaneously breathing, aerosol administration will continue via the handheld adaptor for the remainder of the treatment period.¹⁰²

p - Serum amikacin for trough level will be obtained 30 ± 15 minutes¹⁰³ prior to the first dose on each treatment day. In addition, these trough levels should be obtained for all patients and be sent to the Central Laboratory. If the site has mandated procedures for monitoring IV amikacin treatment, the site should perform these site-specific procedures in conjunction with the collection for serum Amikacin levels.

q – Adverse event reporting begins after the signing of the informed consent by the patient or their authorized representative.

r - Optional assessments

s –¹⁰⁴ An arterial blood gas is needed at the TOC and premature discontinuation visits.

101 As per Amendment 6

102 As per Amendment 6

103 “ ± 15 ” added with Amendment 6

104 Per Amendment 8

15.2 Pulmonary Drug Delivery System (PDDS Clinical)

Figure 1: PDDS Clinical for Ventilator Application

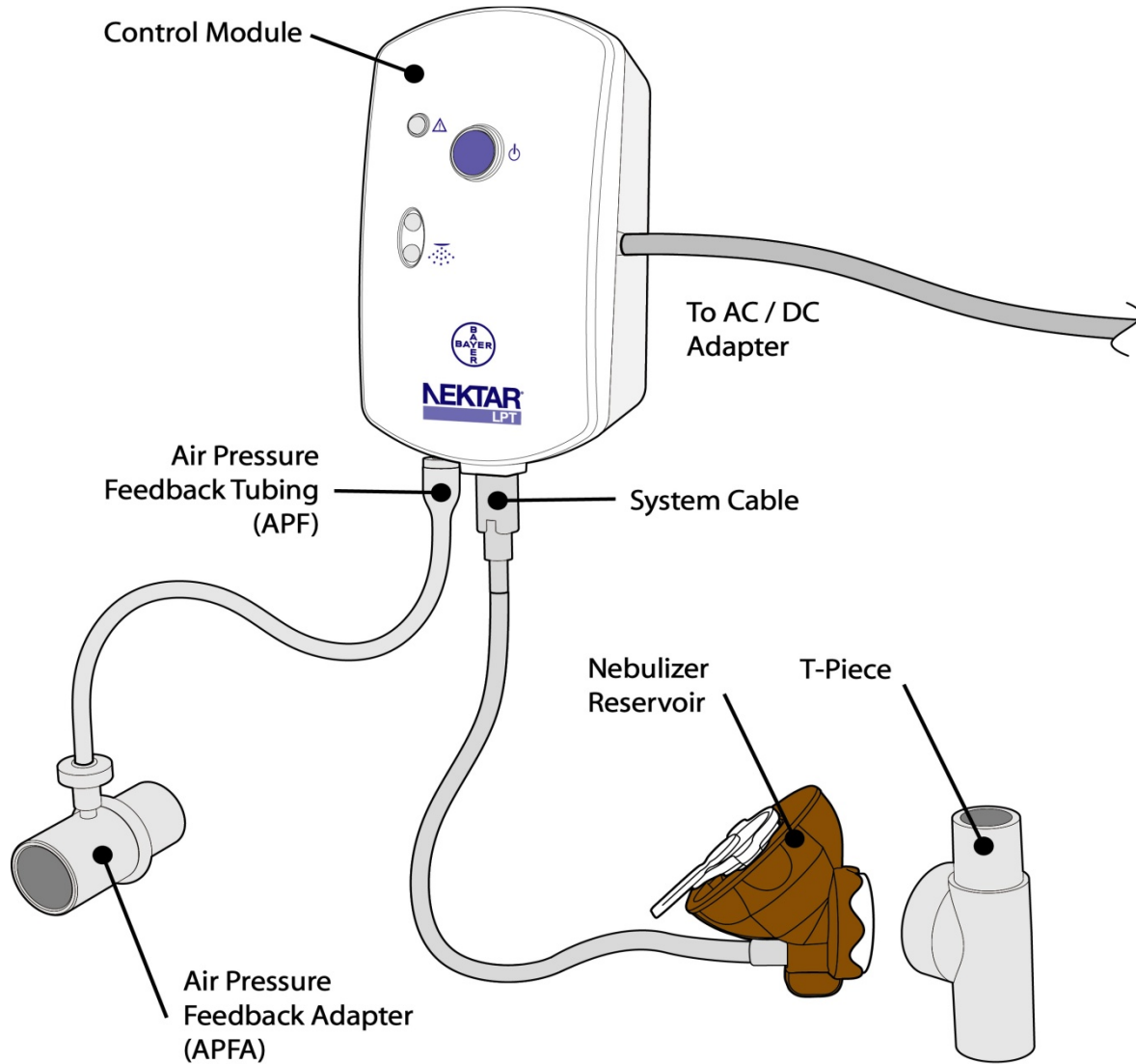


Figure 2: PDDS Clinical on Vent Configuration

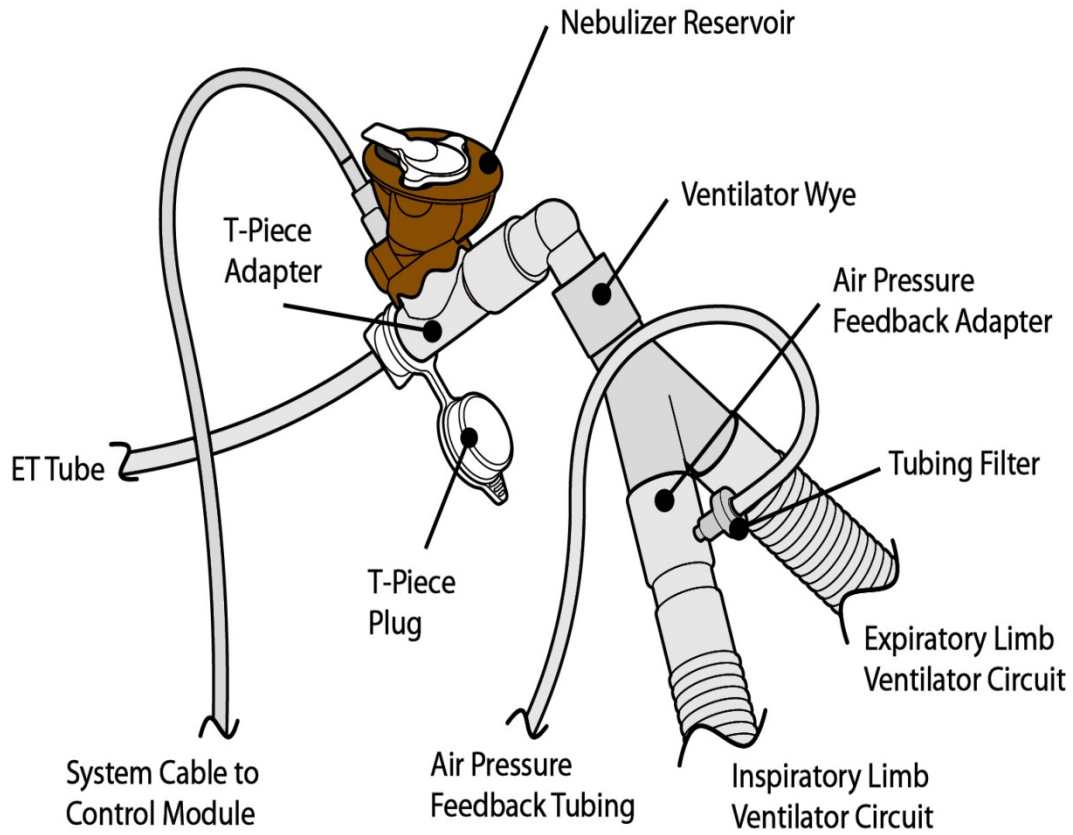
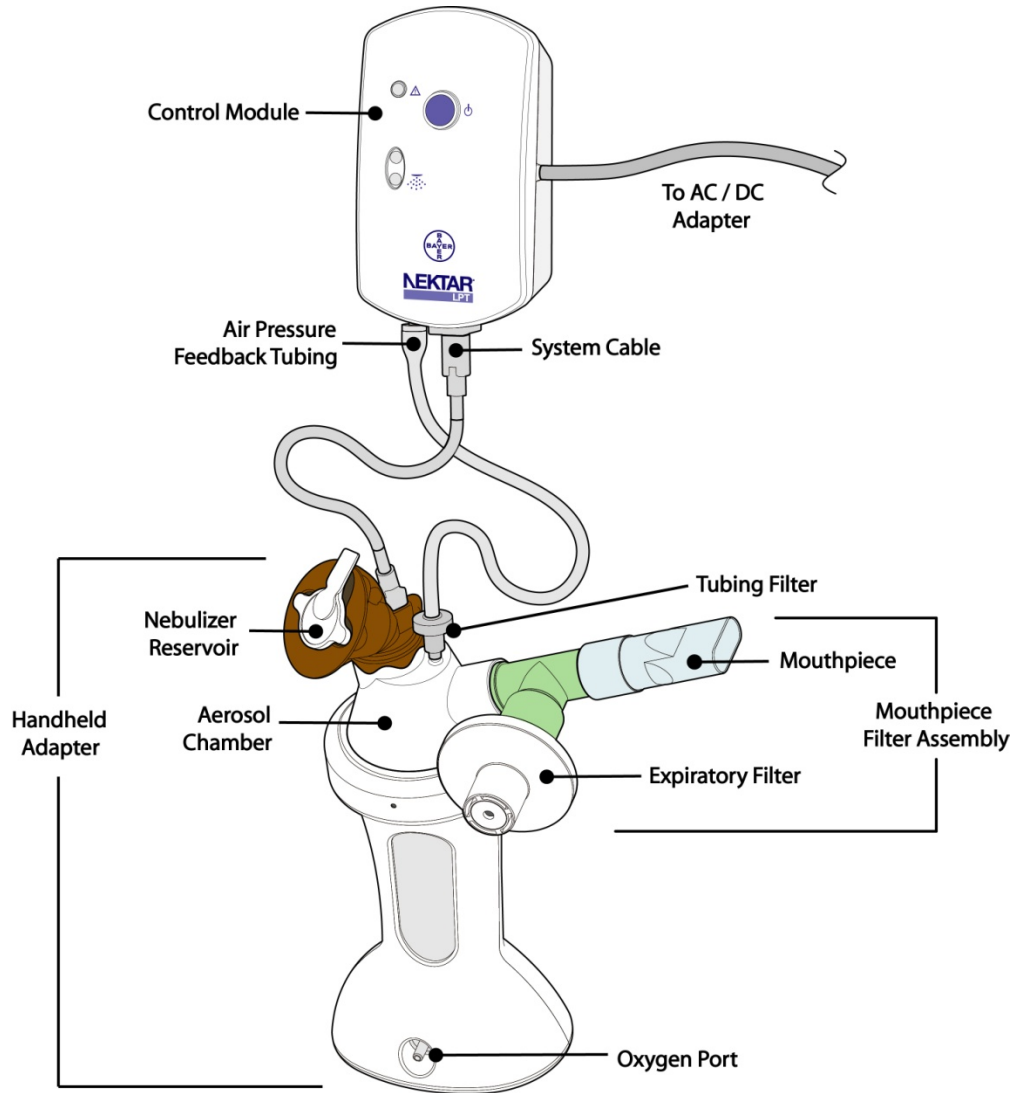


Figure 3: PDDS Nebulizer/Reservoir Inserted Into the Handheld Adaptor



15.3 Clinical Pulmonary Infection Score (CPIS) - amended

CPIS Points	0	1	2
Tracheal secretions	Few (purulent + 1)	Moderate (purulent + 1)	Large (purulent + 1)
Chest radiograph	No infiltrate	Patchy or Diffuse	Localized
Temperature (core), °C ¹⁰⁵	≥ 36.5 and ≤ 38.4	≥ 38.5 and ≤ 38.9	≥ 39.0 or ≤ 36.4
Blood leukocytes, per mm ³	≥ 4,000 and ≤ 11,000	< 4,000 or > 11,000	--
Oxygenation PaO ₂ / FiO ₂ , mm Hg	> 240 or presence of ARDS	--	≤ 240 and absence of ARDS

ARDS – acute respiratory distress syndrome

Guidance for Investigators for Calculating the CPIS

- **Tracheal secretions:** to assign a point score for the quantity and appearance of tracheal secretions observed in the last 24 hours¹⁰⁶, consult the nursing/respiratory therapy notes for the best estimate
 - Add 1 point, if the tracheal secretions are considered purulent (e.g., if the patient had “few” secretions but they were purulent, then the patient would have a score of 1 for this component of the score; or if the patient had a “large” amount of purulent secretions, then the score would be 3)
- **Chest radiograph (CXR):** the most recent CXR taken within the previous 24 hours¹⁰⁶ (or sooner)
- **Temperature, °C:** the maximal temperature taken within the previous 24 hours¹⁰⁶ should be used for point assignment
 - For patients with hypothermia, the lowest temperature taken in the previous 24 hours¹⁰⁶ should be used for point assignment
- **Blood leukocytes (WBC) (cells/mm³):** the maximal WBC count reported in the previous 24 hours¹⁰⁶ should be used for point assignment
 - For patients with leukopenia, the lowest WBC count reported in the previous 24 hours¹⁰⁶ should be used for point assignment
- **Oxygenation PaO₂ / FiO₂, mm Hg:** the most recently calculated P/F ratio obtained within the last 24 hours¹⁰⁶ should be used for point assignment

Note: If an arterial blood gas measurement is not obtained, a PaO₂ value can be derived from pulse oximetry data according to the following method.

¹⁰⁵ Row modified per Amendments 6 and 7

¹⁰⁶ within 48 hours for the screening visit; within 24 hours for all other visits (added per Amendment 6)



If using pulse oximetry, use the SaO₂ to PaO₂ Conversion Table⁴⁸ as shown in Section 15.8.

- Patients who develop ARDS after initiation of study drug should have an oxygenation PaO₂ / FiO₂ score the same as when they developed ARDS ¹⁰⁷
- Patients on veno-arterial (V-A) ECMO prior to randomization should have their oxygenation PaO₂ / FiO₂ scored as 0; patients who initiate V-A ECMO after randomization should have their oxygenation PaO₂ / FiO₂ score maintained throughout as the same value at the time when they initiated V-A ECMO ¹⁰⁸

¹⁰⁷ Per Amendment 5

¹⁰⁸ Per Amendment 5

15.4 National Institute of Health Stroke Scale

Tested Item	Title	Scores and Responses
1A	Level of consciousness	0 – alert 1 – drowsy 2 – obtunded 3 – coma/unresponsive
1B	Orientation questions (2)	0 – answers both correctly 1 – answers one correctly 2 – answers neither correctly
1C	Response to commands (2)	0 – performs both tasks correctly 1 – performs one task correctly 2 – performs neither
2	Gaze	0 – normal horizontal movements 1 – partial gaze palsy 2 – complete gaze palsy
3	Visual fields	0 – no visual field defect 1 – partial hemianopia 2 – complete hemianopia 3 – bilateral hemianopia
4	Facial movements	0 – normal 1 – minor facial weakness 2 – partial facial weakness 3 – complete unilateral palsy
5	Motor function (arm) a. Left b. Right	0 – no drift 1 – drift before 5 seconds 2 – falls before 10 seconds 3 – no effort against gravity 4 – no movement
6	Motor function (leg) a. Left b. Right	0 – no drift 1 – drift before 5 seconds 2 – falls before 10 seconds 3 – no effort against gravity 4 – no movement
7	Limb ataxia	0 – no ataxia 1 – ataxia in 1 limb 2 – ataxia in 2 limbs
8	Sensory	0 – no sensory loss 1 – mild sensory loss 2 – severe sensory loss
9	Language	0 – normal 1 – mild aphasia 2 – severe aphasia 3 – mute or global aphasia
10	Articulation	0 – normal 1 – mild dysarthria 2 – severe dysarthria
11	Extinction of inattention	0 – absent 1 – mild (loss 1 sensory modality) 2 – severe (loss 2 modalities)

Instructions: Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (ie, repeated requests to patient to make a special effort). The score should be assessed within 6 hours of the planned first administration of the study medication and should be compared retrospectively with the score derived following the same scoring system applied to patient's neurological condition 2 days before. Should there be an indication for deterioration - the patient should not be enrolled in the study.

15.5 APACHE II Score / Glasgow Score - amended

The Acute Physiology and Chronic Health Evaluation II is a severity of disease classification system (Knaus et al, 1985)⁴⁶, one of several ICU scoring systems. After admission of a patient to an ICU, an integer score from 0 to 71 is computed based on several measurements; higher scores imply a more severe disease and a higher risk of death.

APACHE II was designed to measure the severity of disease for adult patients admitted to ICUs. The lower age is not specified in the original article, but a good limit is to use APACHE II only for patients age 15 or older.

This scoring system is used in many ways:

- Some procedures and some medicine is only given to patients with certain APACHE II score
- APACHE II score can be used to describe the morbidity of a patient when comparing the outcome with other patients
- Predicted mortalities are averaged for groups of patients in order to specify the group's morbidity.

Even though newer scoring systems, like Simplified Acute Physiology Score (SAPS) II have replaced APACHE II in many institutions, APACHE II continues to be used extensively because so much documentation is based on it.

The point score is calculated from 12 routine physiological measurements (such as blood pressure, body temperature, heart rate etc.).¹⁰⁹ The calculation method is optimized for paper schemas. The resulting point score should always be interpreted in relation to the illness of the patient.

After the initial APACHE II score has been determined, no new score can be entered for this study during the hospital stay.¹¹⁰ If a patient is discharged from the ICU and readmitted, a new APACHE II score can be calculated.

The appendix of the document that originally described the APACHE II score describes how to calculate a predicted death rate for a patient. In order to make this calculation of predicted mortality precise, the principal diagnosis leading to ICU admission was added as a category weight: the predicted mortality is computed based on the patient's APACHE II score and their principal diagnosis at admission.

¹⁰⁹ Per Amendment 6

¹¹⁰ Per Amendment 6

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APACHE II Scoring Tool										
PHYSIOLOGIC VARIABLE		HIGH ABNORMAL RANGE					LOW ABNORMAL RANGE			
		+4	+3	+2	+1	0	+1	+2	+3	+4
1	Temperature rectal (°C)	= 41	39.0-40.9		38.5-38.9	36.0-38.4	34.0-35.9	32.0-33.9	30.0-31.9	= 29.9
2	Mean arterial pressure = (2 x diastolic+ systolic)/3	= 160	130-159	110-129		70-109		50-69		= 49
3	Heart rate (ventricular response)	= 180	140-179	110-139		70-109		55-69	40-54	= 39
4	Respiratory rate (non-ventilated or ventilated)	= 50	35-49		25-34	12-24	10-11	6-9		= 5
5	Oxygenation A-aDO ₂ or PaO ₂ (mmHg) a)FiO ₂ >0.5:record A-aDO ₂	= 500	350-499	200-349		< 200				
	b)FiO ₂ < 0.5,record only PaO ₂					> 70	61-70		55-60	< 55
6	Arterial pH If no ABGs, record serum HCO ₃ below	= 7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	< 7.15
7	Serum Sodium	= 180	160-179	155-159	150-154	130-149		120-129	111-119	= 110
8	Serum Potassium	= 7.0	6.0-6.9		5.5-5.9	3.5-5.4	3.0-3.4	2.5-2.9		< 2.5
9	Serum Creatinine (mg/dl) Double Points for acute renal failure	= 3.5	2.0-3.4	1.5-1.9		0.6-1.4		<0.6		
10	Hematocrit (%)	= 60		50-59.9	46-49.9	30-45.9		20-29.9		< 20
11	White Blood Count	= 40		20.0-39.9	15.0-19.9	3.0-14.9		1.0-2.9		< 1.0
12	Glasgow Coma Scale (Score = 15 minus actual GCS)	15-GCS=								
A	Total Acute Physiology Score (APS)	Sum of the 12 individual variable points =								
*	Serum HCO ₃ (venous-mMol/L) Not preferred, use only if no ABGs	< 52	41.0-51.9		32.0-40.9	22.0-31.9		18.0-21.9	15.0-17.9	< 15.0

Glasgow Coma Scale		B	Age	Point	C	Chronic Health Points	APACHE II Score
Eyes open	Verbal – non-intubated						(sum of A + B + C)
4 - spontaneously	5 - oriented and conversant	Age		Points		If any of the 5 CHE categories is answered with yes give +5 points for non-operative or emergency postoperative patients with immunocompromised or severe organ insufficiency	A APS points
3 - to verbal	4 - disoriented and talks		< 44	0		+2 points for elective postoperative patient with immunocompromised or history of severe organ insufficiency ¹¹¹	+ B Age points
2 - to painful stimuli	3 -inappropriate words		45-54	2	Liver	- Cirrhosis with PHT or encephalopathy	+ C Chronic Health Points
1 - no response	2 -incomprehensible sounds		55-64	3	Cardiovascular	- class IV angina or at rest or with minimal self care activities - chronic hypoxemia or hypercapnia or	_____
Motor response	1 - no response		65-74	5	Pulmonary	polycytaemia of PHT > 40mmHg	= Total APACHE II
6 - to verbal command	Verbal - intubated		> 75	6	Kidney	-chronic peritoneal or haemodialysis	
5 - localizes to pain	5 -seems able to talk				Immune	- immune compromised host	
4 - withdraws to pain	3 -questionable ability to talk						
3 - decorticate	1 -generally unresponsive						
2 - decerebrate							
1 - no response							
			Age points =			Chronic Health Points =	

¹¹¹ Per Amendment 6.

15.6 Late Follow-Up Questionnaire

Patients will be strongly encouraged to return to their study facility for their LFU. This questionnaire needs to be completed whether in-person (ie, face-to-face) or via phone contact with the patient, or the patient's care giver including recording concomitant medication and AEs.

- 1) Have you seen a doctor since your last visit or release from the hospital/clinic?

If yes: Give reason and complete SAE, AE, and Concomitant Medication pages in the CRF (as applicable)

- 2) Have you been hospitalized since your initial release from the hospital/clinic?

If yes: Give reason and complete SAE, AE, and Concomitant Medication pages in the CRF

- 3) Have you been ill or experienced any unwanted health-related signs or symptoms since your last visit or release from the hospital/clinic?

If yes: Give illness and treatment and complete SAE, AE, and Concomitant Medication pages in the CRF

- 4) Since your last visit, what medications have you stopped, what medications have you started and what medications are you continuing - include dose, reason for taking the medication, start and stop dates

- 5) Have you received antimicrobial medication for a pulmonary infection since your last visit?

NOTE: Complete the Clinical Response Assessment for the Late Follow-up Visit

15.7 Guidance on Tracheal Aspirate Sampling Technique

(Adapted from the American Association for Respiratory Care (AARC) Clinical Practice Guideline, 2010)⁴⁷

Tracheal aspiration through a closed or open suction system for Gram-stain, bacterial culture, or amikacin levels will be performed according to the following instructions immediately prior to aspiration:

- Hyperoxygenate the patient with 100% oxygen for greater than 30 seconds prior to the suctioning event by one of the following procedures -
 - Give three to five breaths with the manual resuscitator bag:
 - For patients on greater than 5 centimeters (cm) H₂O ensure the positive end-expiratory pressure (PEEP) level is maintained
 - Adjust the FiO₂ setting on the mechanical ventilator



- If secretions are thick you may instill normal saline (5 mL) into the artificial airway prior to the suctioning event according to your institution’s procedure (let the saline dwell for five seconds prior to suctioning)
- Sterile technique should be employed
- Suction pressure should be set according to your institution’s procedure
- Place the secretion collection trap in line with the suction system to collect the specimen
- Either through a closed or open suction system, insert the suction catheter until resistance is met, and withdraw 1 cm
- Apply suction for up to 15 seconds while withdrawing the catheter
- Hyperoxygenate the patient with 100% oxygen for greater than 30 seconds prior to the suctioning event by one of the following procedures:
 - Give three to five breaths with the manual resuscitator bag
 - For patients on greater than 5 cm H₂O ensure the PEEP (positive end-expiratory pressure) level is maintained
 - Adjust the FiO₂ setting on the mechanical ventilator
- Return patient to their normal ventilator settings
- Seal and label the collection trap and send it to the clinical laboratory for analysis

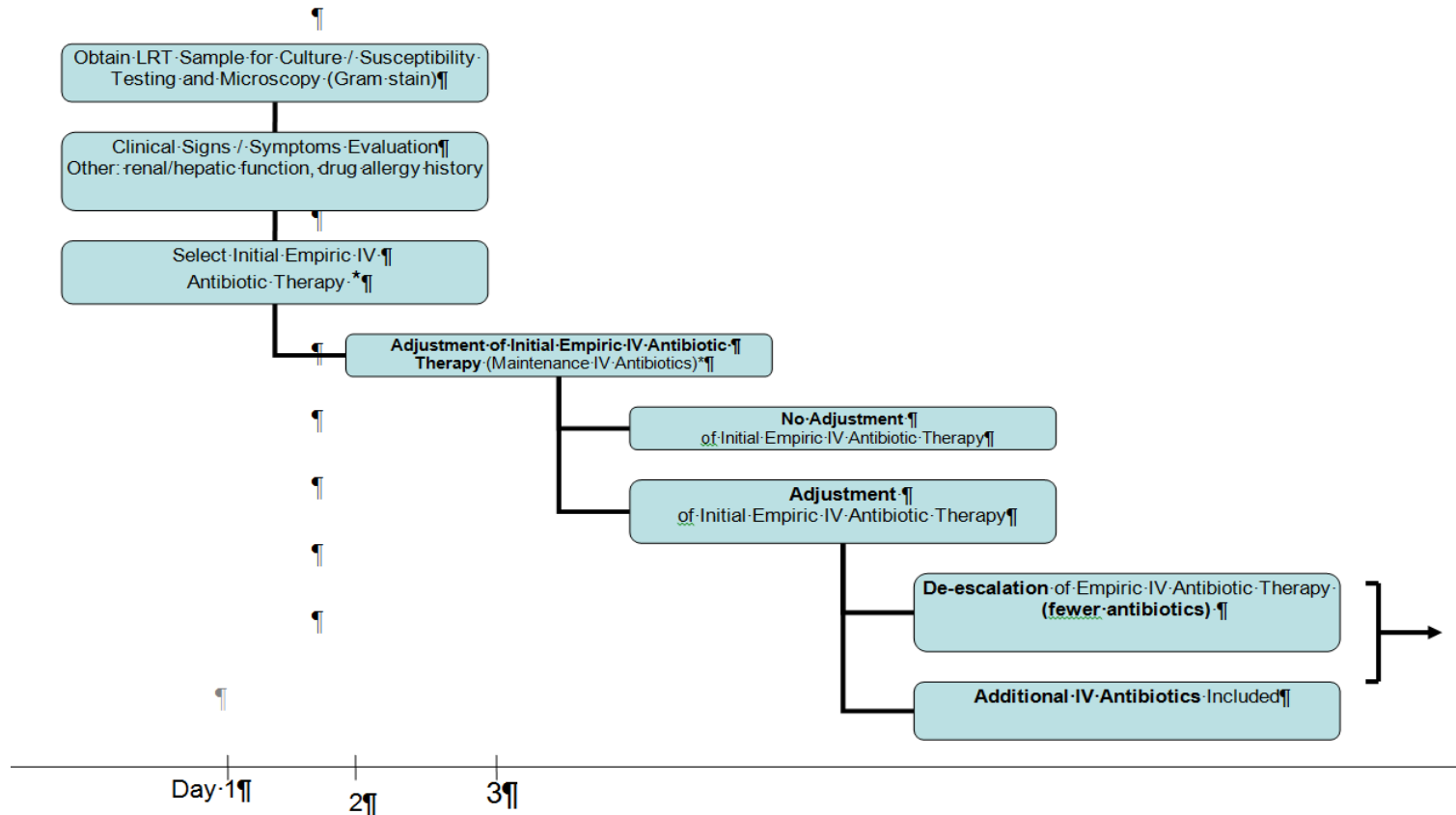
15.8 SpO₂ – Estimated PaO₂ Conversion Table

SpO ₂ Pulse oximeter saturation (%)	Estimated PaO ₂ (mm Hg)
100	265
99	171
98	113
97	91
96	82
95	75
94	69
93	66
92	62
91	60
90	58
89	56
88	54
87	52
86	51
85	50

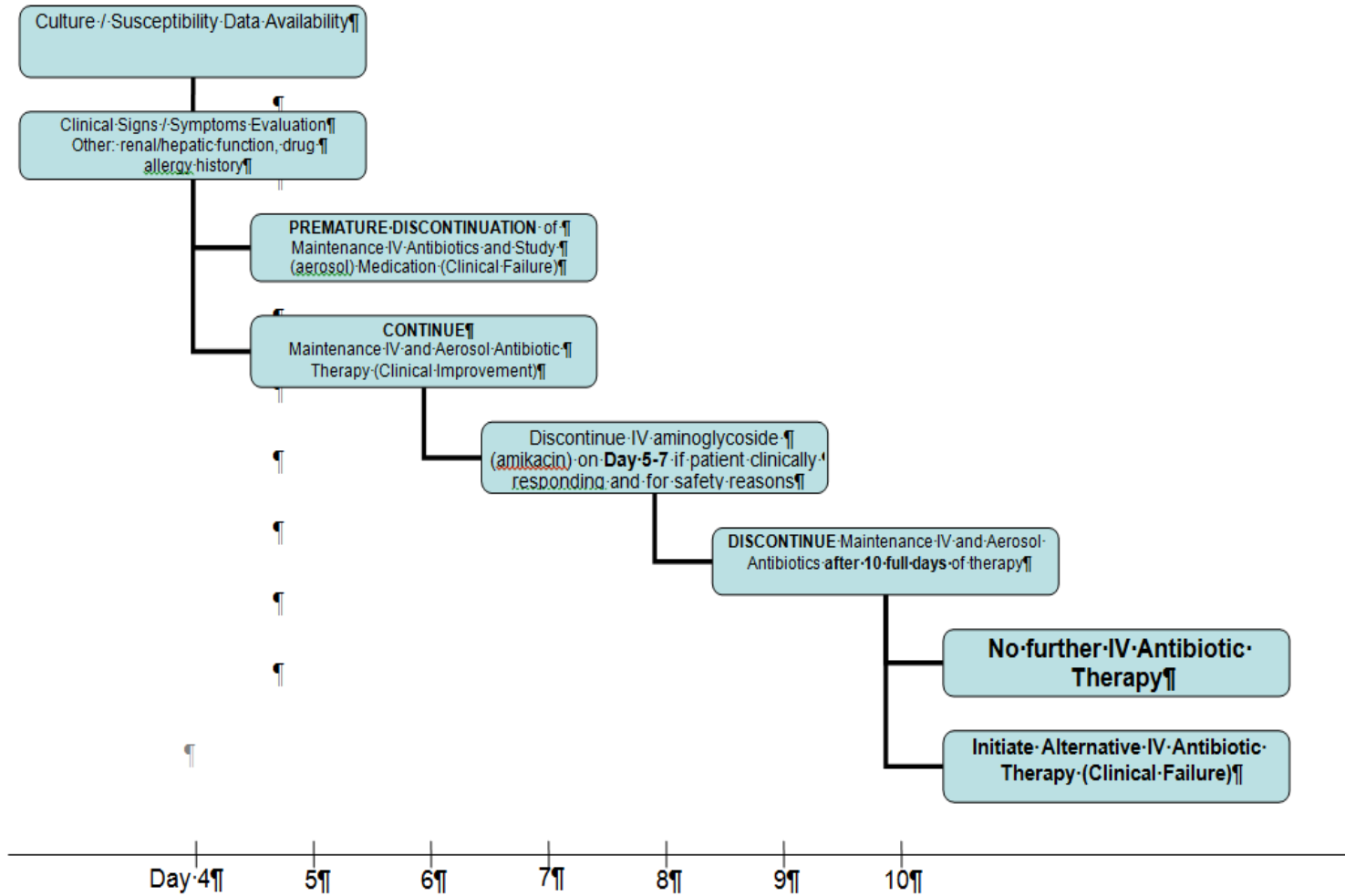


Adapted from Kelman GR. Digital computer subroutine for the conversion of oxygen tension into saturation.
J Appl Physiol 1966 Jul;21(4):1375-6

15.9 Adjustment of Empiric IV Antibiotic Therapy (Treatment Algorithm)



*Adjustment of Initial Empiric IV Antibiotic Therapy is based on the results of culture susceptibility data and/or microscopy, an evaluation of the patient's clinical signs/symptoms of pneumonia (eg, temperature, WBC count with differential, oxygenation, volume and appearance of tracheal secretions, CXR), and other factors such as renal/hepatic function, drug allergy history.



16. Protocol amendments

16.1 Amendment 1

Amendment 1 can be found in integrated protocol version 2.0, dated 17-AUG-2009.

16.2 Amendment 2

Amendment 2 can be found in integrated protocol version 3.0, dated 14-JUN-2010.

16.3 Amendment 3

Amendment 3 can be found in integrated protocol version 4.0, dated 15-MAR-2011.

16.4 Amendment 4

Amendment 4 can be found in integrated protocol version 5.0, dated 31-OCT-2012.

16.5 Amendment 5

Amendment 5 can be found in integrated protocol version 6.0, dated 17 SEP 2014.

16.6 Amendment 6

16.6.1 Overview of Changes

To shorten the time required to develop data from the two Phase III clinical studies of the Amikacin Inhale program (BAY 41-6551/No. 13084 [Inhale 1] and BAY 41-6551/No. 13085 [Inhale 2]) to sustain regulatory submission, Bayer decided that the results of both studies should be consolidated into a single report. This allowed the number of patients required to be reduced from approximately 1300 to approximately 724 in total from both studies.

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 III 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 will require modifications a priority of the statistical analysis plan, but will not require any alterations to patient management, modifications to data collection tools, or changes to the evaluations being performed at the clinic to assess Clinical Failure or Success. The aim is that the patient population recruited to the study and the management of the patients will be the same after the implementation of this amendment as it was before.

The changes to the protocol are summarized below:

- Recruitment will continue in the two Phase III Amikacin Inhale studies until a total of approximately 724 patients have been enrolled. Enrollment will be competitive and both studies will be stopped when that number is reached. The Synopsis and Section 8.3 were revised.
- Text was updated with the latest revision date of the Investigator's Brochure. Sections 5.4.2 and 14 were revised.

- Clarification was made with regards to the presence of Gram-negative organism as an inclusion criterion versus the mITT population evaluation criterion. Section 8.3 was revised.
- The primary efficacy endpoint has been modified so that the antibiotic rules better reflect clinical success or failure and the other variables are more clearly aligned with clinical response. The specific endpoints are as follows:
 - All-cause mortality to Day 28 (previously was to Day 17-19). Pneumonia-related mortality will become an important secondary endpoint.
 - Systemic antibiotic duration to the TOC visit (Day 17-19); all antibiotic adjustments to the TOC visit are allowed, extension or restarting of antibiotics for pneumonia beyond the TOC visit is not allowed.
 - No AE of lung abscess or empyema reported through the LFU visit
 - Stable respiratory function at TOC (new). The assessment will be based on the Berlin Criteria for ARDS, which categorizes severity based on P/F ratios. (49)

The Synopsis, and Sections 5.1, 6, 8.2, 9.6.1, and 14 were revised.

- Sections were moved for better comprehension. The assessments previously referred to as Clinical Response Assessments (renamed as Investigator Assessment of Patient Outcome) were moved from Section 9.6.2.2 to Section 9.6.1.2.
- Changes were made to the statistical sections due to the combining of data from study 13084 and study 13085. Sections 11.1.1, 11.1.2, 11.2, and 11.3 have been modified to reflect the changes to data management and analyses.
- The secondary variables have been revised. Days in hospital and relapses rates have been removed, and pneumonia-related mortality added and speed of response based on CPIS success or failure has been added. The secondary endpoints were changed due to the change in primary endpoints. CPIS, which mainly measures the speed of response, is now removed from consideration in the primary endpoint and has instead been added as an Early Clinical Response component to the secondary endpoints. In addition, pneumonia-related mortality was discussed and suggested as a possible secondary endpoint. These two additions required the removal of the least relevant secondary endpoint. Both relapse rate (success at TOC, but failure by LFU Day 28-32) and hospital days were deemed as less likely to differentiate based on superior versus standard therapy. The Synopsis and Sections 6 and 11.4 were revised.
- An Adjudication Committee will be appointed: there will be 3 members one of whom will be appointed chairman. An Adjudication Committee Charter will be drawn up and guidelines produced that will determine the scope and methods to be applied by the committee. A paragraph was added to Section 7 describing the role of the Adjudication Committee. The Adjudication Committee was added to facilitate the evaluation of mortality data from the different sites. The Adjudication Committee will ensure a standardization of evaluation criteria.
- The instructions for used and unused devices were revised in Sections 8.4.5 and 8.5.3.

- The option of using pulse oximetry at the TOC and premature discontinuation visits was deleted. An arterial blood gas is needed at these visits in order to calculate a PaO₂/FiO₂ ratio required by the new endpoint. Sections 9.1.3.2, 9.5, and 15.1 were updated.
- Missing text was added to the APACHE II Scoring Tool and clarification was added regarding scoring. Section 15.5 was updated.
- Minor editorial changes were made to improve clarity, corrections were made due to inconsistencies, text was revised to correct/clarify the timing of assessments, and terminology was revised for clarity and consistency. The Synopsis, and Sections 4, 5.1, 6, 7, 8.1, 8.2, 8.3.1, 8.3.3.1, 8.4.1, 8.4.5, 9.1.2, 9.1.2.1, 9.1.2.2, 15.1, and 15.3 were revised.
- Lastly, the use of word “subject(s)” was replaced with “patient(s)” in this Phase III protocol.

16.6.2 Changes to the Protocol Text

In this section, all sections affected by this amendment are detailed; the sequence follows the structure of the most recent previous protocol version. Deletions are ~~erossed-out~~ and additions are underlined. Minor editorial changes and corrections of typographical errors are not shown.

Synopsis

Old text:

Study objectives	To evaluate the efficacy (superiority) and safety of BAY 41-6551 as measured by the comparison of the clinical cure rate of aerosolized BAY 41-6551, administered via the PDDS Clinical, versus placebo (normal saline) at the Test of Cure (TOC) visit in patients with microbiologically confirmed Gram negative pneumonia.
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New text:

Study objectives	<u>The study objective is 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. The efficacy endpoint is Clinical Success as defined in Section 8.2. The secondary endpoint objectives are to evaluate the superiority of aerosolized BAY 41-6551 versus aerosolized placebo in pneumonia-related mortality, the Early Clinical Response at Day 10, the days on ventilation, and the days in the ICU.</u>
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Added text:

Safety endpoints	The safety endpoints are to compare (BAY 41-6551 vs <u>aerosolized placebo, as adjunctive therapy to IV antibiotics in both arms</u>) as measured by: <ul style="list-style-type: none">• The frequency of adverse events (AEs)• The progression and incidence rates of organ failure• The all-cause mortality rate during therapy, at Day 15 and at Day 28
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Old text:

Patient population	Adult patients (age ≥ 18 years) with a microbiologically-confirmed pneumonia caused by Gram-negative organisms will be selected for this study.
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New text:

Patient population	<u>Randomized, adult patients (age ≥ 18 years) with a microbiologically-confirmed pneumonia caused by Gram-negative organisms who received at least one dose of study drug and have an APACHE II score ≥ 10 at the time of diagnosis of pneumonia (modified Intent-to-Treat [mITT] population) will be analyzed in the primary efficacy analysis.</u>
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Old text:

Study design	This is a prospective, randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety and efficacy of 10 calendar day (20 doses) course of aerosolized BAY 41-6551 400 mg (amikacin as free base) every 12 hours versus placebo (normal saline) as adjunctive therapy in intubated and mechanically-ventilated patients with Gram-negative pneumonia. All patients will receive parenteral antibiotics according to the 2005 ATS/IDSA guidelines for the management of HAP, VAP, or HCAP for 10 days. Patients who are extubated before completing the full course (10 calendar days if the first dose is administered in the AM or 11 calendar days if the first dose is administered in the PM [20 doses]) of aerosol therapy will be continued on aerosolized therapy with the handheld adaptor. (Section 8.2)
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New text:

Study design	This is a prospective, randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety and efficacy of 10 calendar day (20 doses) course of aerosolized BAY 41-6551 400 mg (amikacin as free base) every 12 hours versus <u>aerosolized placebo (normal saline)</u> , as adjunctive therapy to <u>IV antibiotics in both arms</u> , in intubated and mechanically-ventilated patients with <u>known or suspected</u> Gram-negative pneumonia. All patients will receive parenteral antibiotics <u>with consideration to include 2 antibiotics as per the 2005 ATS/IDSA guidelines for 10 days</u> . Patients who are extubated before completing the full course (10 calendar days if the first dose is administered in the AM or 11 calendar days if the first dose is administered in the PM [20 doses]) of aerosol therapy will be continued on aerosolized therapy with the handheld adaptor. (Section8.2)
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Old text:

Concurrent control	Placebo aerosol solution
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New text:

Concurrent control	<u>Aerosolized placebo</u>
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Old text:

Methodology	Seven to ten days after completing 10 days of aerosolized treatment, patients will be evaluated for clinical response , which will be assessed based on the results of chest x rays, CPIS scores, use of antibiotic therapy, and survival .
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New text:

Methodology	<u>Eighteen to 22</u> days after completing 10 days of aerosolized treatment, patients will be evaluated for Clinical <u>Success</u> , which will be based on survival, the <u>duration</u> of antibiotic therapy, <u>the absence of empyema or lung abscess</u> , and stable respiratory function.
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Old text:

<p>Efficacy variables</p>	<p>The primary efficacy variable will be the clinical response at the TOC visit in the modified Intent to Treat (mITT; ie, ITT population plus a pre-therapy culture positive for a Gram-negative respiratory tract-pathogen and an APACHE II score of ≥ 10) population. The mITT population will be the primary analysis group.</p> <p>The secondary objectives are to evaluate the efficacy of BAY 41-6551 (versus placebo) as measured by:</p> <ul style="list-style-type: none"> • The number of days on mechanical ventilation • The number of ICU days at Day 28 • The total number of days of Gram negative intravenous (IV) antibiotics per patient • CPIS changes through TOC • The clinical relapse rates at Day 28 • The all cause mortality rate during therapy at Day 15 and at Day 28 • The number of hospital days at Day 28
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New text:

<p>Efficacy variables</p>	<p>The primary efficacy variable will be <u>Clinical Success</u> in the mITT population (ie, <u>the ITT population who prove to be culture positive for a Gram-negative pathogen and have an APACHE II score ≥ 10</u>). <u>Clinical Success is achieved when all of the following criteria are met:</u></p> <ol style="list-style-type: none"> <u>1) Systemic antibiotics (IV or by mouth [PO] for pneumonia must be stopped on or before the Test-of-Cure (TOC) visit (Day 17-19)</u> <u>2) Systemic antibiotics (IV or PO) for pneumonia must not be restarted after the TOC visit</u> <u>3) The patient must survive through the late follow-up (LFU) visit</u> <u>3) The patient must not have a reported AE of lung abscess or empyema through the LFU visit and</u> <u>4) The patient must have stable respiratory function measured at the TOC visit</u> <p>The secondary objectives are to evaluate the efficacy of BAY 41-6551 (versus <u>aerosolized placebo</u>), <u>as adjunctive therapy to IV antibiotics in both arms</u>, as measured by:</p> <ul style="list-style-type: none"> • <u>Pneumonia-related mortality to the LFU visit</u> • <u>Early Clinical Response based on CPIS scores, the presence of empyema or lung abscess, and all-cause mortality through Day 10</u> • <u>The number of days on mechanical ventilation through the LFU visit (Day 28-32)</u> • <u>The number of ICU days assessed at the LFU visit (Day 28-32)</u> <p><u>The investigator will assess patient signs and symptoms at the TOC visit (Day 17-19) for the Investigator Assessment of Patient Outcome, which is separate from the primary efficacy variable, Clinical Success.</u></p>
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Old text:

<p>Microbiology variables</p>	<p>Secondary microbiological objectives will include comparisons (aerosolized BAY 41-6551 versus placebo) of the:</p> <ul style="list-style-type: none"> • per pathogen microbiological response rates at the TOC visit • per patient microbiological response rate at the TOC visit • microbiological recurrence rates at the TOC and Day 28 visit • emergence of new respiratory pathogens during the treatment period • emergence of resistance among baseline pathogens in those patients with persistent infection or colonization
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New text:

<p>Microbiology variables</p>	<p>Secondary microbiological objectives will include comparisons (aerosolized BAY 41-6551 versus <u>aerosolized placebo</u>), <u>as adjunctive therapy to IV antibiotics in both arms</u>, of the:</p> <ul style="list-style-type: none"> • per pathogen microbiological response rates at the TOC visit • per patient microbiological response rate at the TOC visit • microbiological recurrence rates at the TOC and <u>LFU visits</u> • emergence of new respiratory pathogens during the <u>aerosol treatment period, Day 1-10</u> • emergence of resistance among baseline pathogens in those patients with persistent infection or colonization
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Old text:

<p>Total number of patients</p>	<p>Approximately 662 patients will be randomized 1:1 to receive either 400 mg BAY 41-6551 (amikacin as free base) every 12 hours or placebo every 12 hours in addition to ATS/IDSA guided IV antibiotic therapy to allow for completion of at least 430 evaluable patients in the primary efficacy analysis.</p>
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New text:

<p>Total number of patients</p>	<p>Approximately <u>a combined total of 724 ITT patients will be recruited to this study and to study 13085 (being conducted in different countries; the protocols are identical with the exception that study 13085 has a pharmacokinetic substudy). The 724 total patients will be recruited competitively between studies 13084 and 13085; there are no minimum requirements for recruitment totals in either study. The patients</u> will be randomized 1:1 to receive either 400 mg BAY 41-6551 (amikacin as free base) every 12 hours or <u>aerosolized placebo every 12 hours in addition to ATS/IDSA guided IV antibiotic therapy to allow for completion of at least 472</u> evaluable <u>mITT</u> patients in the primary efficacy analysis.</p>
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4. Glossary and Abbreviations

Old text:

ICH	International Conference on Harmonization
PDDS Clinical	Pulmonary Drug Delivery System

New text:

ICH	International <u>Council for</u> Harmonization
PDDS	Pulmonary Drug Delivery System
<u>P/F</u>	<u>PaO₂/FiO₂</u>

5.1 Background and Rationale

Old text: (last paragraph)

This clinical study will evaluate the ~~clinical cure~~ rate of ~~adjunctive~~ aerosolized amikacin, administered via PDDS Clinical, to that of placebo (normal saline solution) ~~at the Test of Cure (TOC) visit~~ in patients with microbiologically-confirmed Gram-negative pneumonia.

New text: (last paragraph)

This clinical study will evaluate the Clinical Success rate of aerosolized amikacin, administered via PDDS Clinical, to that of aerosolized placebo (normal saline solution), as adjunctive therapy to IV antibiotics in both arms, in patients with microbiologically-confirmed Gram-negative pneumonia.

5.4.2 Human Studies

Deleted text: (last paragraph)

Further details on the five clinical studies completed with BAY 41-6551 can be found in the Investigator's Brochure (~~23 APR 2014 Ver. 3.0~~).

6. Study Objectives

Old text:

~~6.1 Primary Objective~~

~~To evaluate the efficacy (superiority) and safety of BAY 41-6551 as measured by the comparison of the clinical cure rate of aerosolized BAY 41-6551, administered via the PDDS~~

~~Clinical, versus placebo (normal saline) at the TOC visit in patients with microbiologically confirmed Gram-negative pneumonia.~~

~~6.2 Secondary Objectives~~

~~The secondary objectives are to evaluate the efficacy of BAY 41-6551 (versus placebo) as measured by:~~

- ~~• The number of days on mechanical ventilation~~
- ~~• The number of ICU days at Day 28~~
- ~~• The total number of days of Gram-negative IV antibiotics per patient~~
- ~~• CPIS changes through TOC~~
- ~~• The clinical relapse rates at Day 28~~
- ~~• The all-cause mortality rate during therapy, at Day 15 and at Day 28~~
- ~~• The number of hospital days at Day 28~~

~~6.3 Additional Objective~~

~~To determine that the PDDS Clinical device performs as intended.~~

~~6.4 Safety Endpoints~~

~~The safety endpoints are to compare (BAY 41-6551 vs placebo) as measured by:~~

- ~~• The frequency of AEs~~
- ~~• The progression and incidence rates of organ failure~~
- ~~• The all-cause mortality rate during therapy, at Day 15 and at Day 28~~

New text:

The study objective is 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. The efficacy endpoint is Clinical Success as defined in Section 8.2. The secondary objectives are to evaluate the superiority of aerosolized BAY 41-6551 versus aerosolized placebo in pneumonia-related mortality to the LFU visit, the Early Clinical Response at Day 10, the days on ventilation through the LFU visit, and the days in the ICU assessed at the LFU visit.

7. Investigators and Other Study Participants

Old text: (1st paragraph)

The ^{PPD} [REDACTED] The role of the coordinating investigator has been assigned to Michael S. Niederman, MD, Winthrop University Hospital, ^{PPD} [REDACTED]

New text: (1st paragraph)

The ^{PPD} [REDACTED] The role of the coordinating investigator has been assigned to Michael S. Niederman, MD, New York-Presbyterian University Hospital of Columbia and Cornell. ^{PPD} [REDACTED]

Added text: (3rd paragraph)

Bayer will utilize an independent Adjudication Committee for the evaluation of the secondary variable, pneumonia-related mortality. The Adjudication Committee will be comprised of 3 clinicians experienced in the field of clinical research and anti-infective drug products. Each committee member will be screened for evidence of an absence of serious conflicts of interest. The operation of the Adjudication Committee will be governed by a charter.

Added text (after 3th paragraph)

In brief, the adjudication committee will review all deaths to determine the subset of deaths that are pneumonia-related. These pneumonia-related deaths should more likely be influenced by superior antibacterial treatment than pneumonia-unrelated deaths. The pneumonia-related death evaluation will be based on the death being plausibly related to:

- (1) pulmonary infection (example pneumonia)
- (2) spread (metastasis) of infection (example septicemia, septic shock)
- (3) complications related to respiratory function. (example respiratory distress)

The AC will have a single binary decision: pneumonia-related death: yes/no

8.1 Study Design

Old text:

This is a Phase III, prospective, randomized, double-blind, placebo-controlled, multicenter, multinational study designed to show that aerosolized BAY 41-6551 400 mg (amikacin as free base) every 12 hours is more effective than placebo (aerosolized normal saline) as adjunctive therapy in intubated and mechanically-ventilated patients with Gram-negative pneumonia. The safety and tolerability of aerosolized BAY 41-6551 and the microbiological endpoints will also be evaluated. Patients who are extubated before completing the full course (10 calendar days if the first dose is administered in the AM or 11 calendar days if the first dose is administered in the PM [20 doses, Section 8.2]) of aerosol therapy will be continued on aerosolized BAY 41-6551 with the handheld adaptor. All patients will receive standard of care IV antibiotic therapy ~~guided by the ATS/IDSA Guidelines for the management of adults with HAP, VAP, and HCAP.~~

New text:

This is a Phase III, prospective, randomized, double-blind, placebo-controlled, multicenter, multinational study designed to show that aerosolized BAY 41-6551 400 mg (amikacin as free base) every 12 hours is more effective than placebo (aerosolized normal saline), as adjunctive therapy to IV antibiotics in both arms, in intubated and mechanically-ventilated

patients with Gram-negative pneumonia. The safety and tolerability of aerosolized BAY 41-6551 and the microbiological endpoints will also be evaluated. Patients who are extubated before completing the full course (10 calendar days if the first dose is administered in the AM or 11 calendar days if the first dose is administered in the PM [20 doses, Section 8.2]) of aerosol therapy will be continued on aerosolized BAY 41-6551 with the handheld adaptor. All patients will receive standard of care IV antibiotic therapy with consideration to include 2 antibiotics as per the ATS/IDSA Guidelines.

8.2 Study Plan

Old text:

The TOC visit will be conducted on Day 17-19 of the study ~~or at the time the patient is considered a treatment failure and/or study drug is prematurely discontinued.~~ The late follow-up visit will be conducted on Day 28-32 of the study. Clinical response will be evaluated at the TOC and late follow-up visits (Sections 9.6.1.2.2 and 9.6.1.2.3). If available, respiratory secretions will be obtained, cultured, and evaluated for the emergence of resistance to study drug therapy among baseline organisms.

The definition of Clinical Failure at the TOC visit will be

- ~~• A rise in the CPIS by at least 2 points on Day 3~~
- ~~• Failure of the CPIS to drop at least 1 point on Day 5~~
- ~~• Failure of the CPIS to drop by at least 2 points on Day 10~~
- ~~• Continuation of systemic antibiotics (IV or by mouth [PO]) for pneumonia after ten full days of aerosolized dosing~~
- ~~• Restarting systemic antibiotics (IV or PO) for pneumonia before the TOC (with a positive respiratory culture) visit;~~
- ~~• One adjustment to the antimicrobial regimen is allowed when the initial culture result susceptibility results are available (typically 48-72 hours). Any additional change to the antimicrobial regimen being used to treat pneumonia during the first 10 days, after the initial antimicrobial adjustment of empiric therapy as soon as initial culture and susceptibility results are available, would be considered a Clinical Failure. There are two exceptions where additional changes to the antimicrobial regimen are not considered Clinical Failures:
 - ~~○ 1) discontinuation of IV administered aminoglycosides after 5-7 days or~~
 - ~~○ 2) suitable de-escalation of therapy in patients who are doing well clinically. Suitable de-escalation is either discontinuation or reduction in dose of an anti-infective drug. The initial IV administered gram-negative anti-infective therapy should be maintained for 10 to 12 days.~~~~

~~Patients who discontinue IV administered aminoglycosides after 5-7 days or who are suitably de-escalated are not considered Clinical Failures. Any~~

~~introduction of a new anti-infective drug to treat the pneumonia after the initial adjustment will be considered a treatment failure.~~

~~OR~~

- ~~• All-cause mortality~~

~~Note: At least one of the above conditions is necessary to consider a patient a Clinical Failure.~~

Local microbiology laboratories will perform Gram stains, identify organisms to genus and species (this information will be recorded in the case report form [CRF]) and when performing susceptibility testing will include amikacin in the sensitivity panel. The local microbiology laboratories will send a slide (air dried, ~~but~~ not stained) of the clinical specimen (examples tracheal aspirate, sputum) to the Central Microbiology Laboratory. Instructions for preparing and shipping the slide will be provided in the investigator Manual for Microbiology. ...

New text:

The Test-of Cure (TOC) visit will be conducted on Day 17-19 of the study. The late follow-up (LFU) visit will be conducted on Day 28-32 of the study. Clinical Success will be evaluated at the TOC and LFU visits by programmed response criteria. If available, respiratory secretions will be obtained, cultured, and evaluated for the emergence of resistance to study drug therapy among baseline organisms.

The primary efficacy evaluation of the study is the Clinical Success in the mITT population, which is achieved when the following 5 criteria are met:

- Systemic antibiotics (IV or by mouth [PO]) for pneumonia must be stopped on or before the TOC visit
- Systemic antibiotics (IV or PO) for pneumonia must not be restarted after the TOC visit
- The patient must survive through the LFU visit
- The patient must not have a reported AE of lung abscess or empyema through the LFU visit
- The patient must have stable respiratory function at the TOC visit

Stable or unstable respiratory function is determined based on the PaO₂/FiO₂ (P/F) ratio at TOC in the following manner:

Stable respiratory function:

- Patient is extubated at the TOC visit OR
- Patient is intubated at the TOC visit AND:
 - Patient has a P/F ratio > 200 at the TOC visit OR
 - Patient has a P/F ratio > 100 and ≤ 200 at the TOC visit AND:

- Patient had a P/F ratio \leq 200 at baseline

Unstable respiratory function

- Patient has a P/F ratio \leq 100 at the TOC visit OR
- Patient has a P/F ratio $>$ 100 or \leq 200 at the TOC visit AND:
 - Patient had a P/F ratio $>$ 200 at baseline

The outcome is Clinical Success if all 5 criteria are met. If any one of the criteria is not met, then the patient is considered a Clinical Failure. Patients who do not have a clinical assessment of success due to missing data will be considered a Clinical Failure.

Local microbiology laboratories will perform Gram stains, identify organisms to genus and species (this information will be recorded in the case report form [CRF]) and when performing susceptibility testing will include amikacin in the sensitivity panel. The local microbiology laboratories will send a slide (air dried and not stained) of the clinical specimen (examples tracheal aspirate, sputum) to the Central Microbiology Laboratory. Instructions for preparing and shipping the slide will be provided in the investigator Manual for Microbiology. ...

8.3 Selection of Study Population

Old text:

Patients of age 18 and older, who are hospitalized, have pneumonia suspected or confirmed to be caused by Gram-negative organisms, and who are intubated and mechanically-ventilated will be selected for this study. In all patients where the pathogen is suspected of being Gram-negative, it should be confirmed as soon as culture results are available. Patients with microbiologically-confirmed pneumonia are those who have a Gram-negative organism cultured from an appropriate respiratory tract specimen ~~collected prior to enrollment~~.

The patient must meet all of the inclusion criteria and none of the exclusion criteria to participate in this study. Approximately ~~662~~ patients will be randomized 1:1 to receive either BAY 41-6551 400 mg (amikacin as free base) aerosolized every 12 hours or aerosolized placebo every 12 hours in addition to ATS/IDSA-guided IV therapy to allow for completion of at least ~~430~~ evaluable patients in the primary efficacy analysis.

New text:

Patients of age 18 and older, who are hospitalized, have pneumonia suspected or confirmed to be caused by Gram-negative organisms, and who are intubated and mechanically-ventilated will be selected for this study. In all patients where the pathogen is suspected of being Gram-negative, it should be confirmed as soon as culture results are available. Patients with microbiologically-confirmed pneumonia are those who have a Gram-negative organism cultured from an appropriate respiratory tract specimen.

The patient must meet all of the inclusion criteria and none of the exclusion criteria to participate in this study. Approximately 724 patients will be randomized 1:1 in the 2 Phase III studies (13084 and 13085; study 13085 is being conducted in different countries; the

protocols are identical with the exception that study 13085 has a pharmacokinetic substudy) to receive either BAY 41-6551 400 mg (amikacin as free base) aerosolized every 12 hours or aerosolized placebo every 12 hours in addition to ATS/IDSA-guided IV therapy to allow for completion of at least 472 evaluable patients (mITT) in the primary efficacy analysis.

8.3.1 Inclusion Criteria

Old text:

- 6) Impaired oxygenation (within 24 hours prior to screening): a $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg

New text:

- 6) Impaired oxygenation (within 48 hours prior to screening): a $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg

8.3.3.1 Reasons for Premature Discontinuation of the Study Drug

Added text: (last sentence)

The disposition of patients who are prematurely discontinued is listed in Section 11.3.

8.4.1 Treatments to be Administered

Old text:

Treatment will consist of standard of care IV antibiotics for intubated patients with Gram-negative pneumonia with consideration to include 2 antibiotics ~~according to the 2005~~ ATS/IDSA Guidelines, plus aerosolized BAY 41-6551 or aerosolized placebo (Section 8.2). If the patient develops a new infection, other than pneumonia, while on the aerosol treatment the patient will continue in the study ~~as long as the study treatment for the new infection would not require an antibiotic course longer than the 10-12 full days of IV treatment required by the protocol. Patients should continue aerosol study treatment.~~

Each inhalation or aerosol dose will be administered via the PDDS Clinical (instruction manual provided). If a patient is subsequently extubated, the aerosol treatment will be continued via the handheld adaptor for the remainder of the 10 full days of treatment course. Extending the IV antibiotic therapy beyond the aerosolized therapy might be necessary if in the opinion of the investigator, the patient continues to have clinical signs and symptoms of pneumonia (~~ie, the patient is evaluated as a Clinical Failure~~). The clinical signs and symptoms of pneumonia will be documented on the CRF as will the reason(s) for continuation of IV treatment past the treatment period ~~allowed in the protocol~~. Aerosol treatment will not extend beyond 10 full days corresponding to 20 doses (Section 8.2).

The administration of aerosolized antibiotics other than the aerosol study medication is prohibited.

The use of an IV aminoglycoside during the treatment period will be permitted; however, the only aminoglycoside will be amikacin. This will simplify aminoglycoside trough serum level monitoring, if an IV aminoglycoside is used with the aerosol study drug. The monitoring of a single aminoglycoside (amikacin) will allow for safer use of IV therapy, if IV aminoglycoside therapy is required.

....

New text:

Treatment will consist of standard of care IV antibiotics for intubated patients with Gram-negative pneumonia with consideration to include 2 antibiotics as per the 2005 ATS/IDSA Guidelines, plus aerosolized BAY 41-6551 or aerosolized placebo (Section 8.2). If the patient develops a new infection, other than pneumonia, while on the aerosol treatment the patient will continue in the study.

Each inhalation or aerosol dose will be administered via the PDDS Clinical (instruction manual provided). If a patient is subsequently extubated, the aerosol treatment will be continued via the handheld adaptor for the remainder of the 10 full days of treatment course. Extending the IV antibiotic therapy beyond the aerosolized therapy might be necessary if in the opinion of the investigator, the patient continues to have clinical signs and symptoms of pneumonia. The clinical signs and symptoms of pneumonia will be documented on the CRF as will the reason(s) for continuation of IV treatment past the treatment period. Aerosol treatment will not extend beyond 10 full days corresponding to 20 doses (Section 8.2).

The administration of aerosolized antibiotics other than the aerosol study medication is prohibited.

The use of an IV aminoglycoside during the treatment period will be permitted; however, the only aminoglycoside allowed will be amikacin. This will simplify aminoglycoside trough serum level monitoring, if an IV aminoglycoside is used with the aerosol study drug. The monitoring of a single aminoglycoside (amikacin) will allow for safer use of IV therapy, if IV aminoglycoside therapy is required.

....

Section 8.4.1.1.4 Adjustment of Empiric Intravenous Antibiotic Therapy

Added extra wording to the bullet on maintenance antibiotic therapy

Old text:

Further adjustments to maintenance antibiotic therapy are NOT permitted during the remaining treatment unless the patient is failing antibiotic treatment for pneumonia, (in which case the patient would be considered a failure).

New text:

Further adjustments to maintenance antibiotic therapy are not permitted during the remaining treatment unless the patient is failing antibiotic treatment for pneumonia, in which case the

patient would be considered a failure by the Investigator Assessment (not by the primary endpoint evaluation of Clinical Success).

Section 8.4.5 Administration and Dosing Regimen

Old text:

Dosing of BAY 41-6551 by inhalation will be every 12 hours for ten full days according to Table 4. All investigators should be aware that 400 mg every 12 hours dose of aerosolized BAY 41-6551 refers to the quantity of amikacin free base in BAY 41-6551 Solution (Amikacin Inhalation Solution) delivered from the extractable volume of 3.2 mL and that all blinded medication will be labeled according to the concentration of amikacin free base (125 mg/mL) in BAY 41-6551 Solution (Amikacin Inhalation Solution). Aerosolized therapy will begin within 24 hours of the initiation of IV antibiotics for Gram-negative pneumonia.

...

Used devices will be inventoried and returned to the sponsor or its designee. ~~Unused devices will be inventoried and returned to the sponsor or its designee or be destroyed by the site or by the Bayer local affiliate or its designee.~~

New text:

Dosing of BAY 41-6551 by inhalation will be every 12 hours for ten full days according to Table 4. All investigators should be aware that 400 mg every 12 hours dose of aerosolized BAY 41-6551 refers to the quantity of amikacin free base in BAY 41-6551 Solution (Amikacin Inhalation Solution) delivered from the extractable volume of 3.2 mL and that all blinded medication will be labeled according to the concentration of amikacin free base (125 mg/mL) in BAY 41-6551 Solution (Amikacin Inhalation Solution). Aerosolized therapy will begin within 48 hours of the initiation of IV antibiotics for Gram-negative pneumonia.

...

Used devices identified on the random planned return list will be inventoried and returned to the sponsor or its designee. Used devices not on the planned return list as well as unused devices will be inventoried and destroyed on site or returned to the sponsor or its designee where required by site SOP.

8.5.3 Device Supply

Added text: (3rd paragraph)

Used devices identified on the random planned return list will be inventoried and returned to the sponsor or sponsor's designee.

Section 9.1.2 Treatment Period (Day 1 to Day 10)

Added text: (1st paragraph)

Day 1 is defined as the day the initial dose of study medication (aerosolized BAY 41-6551 or aerosolized placebo) is given. Day 1 ...

Old text: (second bullet)

Patients will be started on aerosolized study medication within 24 hours of IV antibiotic therapy being initiated for Gram-negative pneumonia. Patients will ...

New text: (second bullet)

Patients will be started on aerosolized study medication within 48 hours of IV antibiotic therapy being initiated for Gram-negative pneumonia. Patients will ...

Section 9.1.2.1 Assessments Performed Daily

Added text:

....

Patients not receiving IV amikacin therapy but receiving aerosol treatment will have amikacin serum levels monitored through the Central Laboratory, therefore, a serum amikacin sample should be sent to the Central Laboratory. However, because of low systemic exposure following aerosol treatment, amikacin serum levels will not be reported to the investigator or sub-investigator(s).

- Measurement of serum amikacin trough level 30 minutes (\pm 15 mins) prior to each first aerosol dose of the day.

Section 9.1.2.2 Assessments Performed on Days 1, 3, 5, and 7

Deleted text:

- ~~Measurement of serum amikacin trough level 30 minutes (\pm 15 mins) prior to each first aerosol dose of the day.~~

~~**NOTE:** The laboratory conducting the safety monitoring of serum amikacin trough levels will notify the investigator of the amikacin serum concentration only if the patient is receiving IV amikacin.~~

Section 9.1.3.1 End of Treatment (EOT) Visit (Day 10)

Old text:

The EOT visit will be conducted on Day 10 or within 24 hours after completion of study drug. ~~Clinical cure rates will be evaluated by an assessment~~ of clinical signs and symptoms.

Patients will have the following assessments and procedures performed during the EOT visit:

- A physical examination including vital signs

- CXR obtained

NOTE: the reading and interpretation of the CXR by the investigator and/or sub-investigator(s) at the EOT visit can be used to determine ~~clinical response to therapy~~; however, the radiology report (i.e., the reading and interpretation of the CXR by the Radiologist) will be the “official” reading recorded on the CRF and used for the determination of evaluability. The radiologist will remain blinded to the treatment assignment of the patient.

....

New text:

The EOT visit will be conducted on Day 10 or within 24 hours after completion of study drug. The Investigator Assessment of Patient Outcome will involve an evaluation of clinical signs and symptoms.

Patients will have the following assessments and procedures performed during the EOT visit:

- A physical examination including vital signs
- CXR obtained

NOTE: the reading and interpretation of the CXR by the investigator and/or sub-investigator(s) at the EOT visit can be used to determine the Investigator Assessment of Patient Outcome; however, the radiology report (i.e., the reading and interpretation of the CXR by the Radiologist) will be the “official” reading recorded on the CRF and used for the determination of evaluability. The radiologist will remain blinded to the treatment assignment of the patient.

....

Section 9.1.3.2 Test-of-Cure (TOC) Visit (Days 17 – 19)

Old text:

The TOC visit will be conducted on Days 17-19 of the study. ~~Clinical cure rate will be evaluated~~ by an assessment of clinical signs and symptoms.

....

- **NOTE:** the reading and interpretation of the CXR by the investigator and/or sub-investigator(s) at the TOC visit can be used to determine ~~clinical response to therapy~~; however, the radiology report (ie, the reading and interpretation of the CXR by the radiologist) will be the "official" reading recorded on the CRF and used for the determination of evaluability. The radiologist will remain blinded to the treatment assignment of the patient.

....

- Arterial blood gas ~~or pulse oximetry (arterial blood gases preferred)~~

....

New text:

The TOC visit will be conducted on Days 17-19 of the study. The Investigator Assessment of Patient Outcome will be determined by an assessment of clinical signs and symptoms.

....

- **NOTE:** the reading and interpretation of the CXR by the investigator and/or sub-investigator(s) at the TOC visit can be used to determine the Investigator Assessment of Patient Outcome; however, the radiology report (ie, the reading and interpretation of the CXR by the radiologist) will be the "official" reading recorded on the CRF and used for the determination of evaluability. The radiologist will remain blinded to the treatment assignment of the patient.

....

- Arterial blood gas

....

Section 9.1.3.3 Late Follow-Up Visit (Days 28-32)

Old text:

....

- ~~Clinical response will be evaluated~~ by an assessment of clinical signs and symptoms.

....

New text:

....

- The Investigator Assessment of Patient Outcome will be determined by an assessment of clinical signs and symptoms.

....

Section 9.5 Premature Discontinuation / Early Withdrawal from Study

Old text:

....

- **NOTE:** the reading and interpretation of the CXR by the investigator and/or sub-investigator(s) can be used to ~~for clinical decision-making~~; however, the radiology report (ie, the reading and interpretation of the CXR by the radiologist) will be the "official" reading recorded on the CRF. The radiologist will remain blinded to the treatment assignment of the patient.

....

- Arterial blood gas or pulse oximetry (arterial blood gases are preferred)

....

New text:

....

- **NOTE:** the reading and interpretation of the CXR by the investigator and/or sub-investigator(s) can be used to determine the Investigator Assessment of Patient Outcome; however, the radiology report (ie, the reading and interpretation of the CXR by the radiologist) will be the "official" reading recorded on the CRF. The radiologist will remain blinded to the treatment assignment of the patient.

....

- Arterial blood gas

....

Section 9.6.1 Efficacy Variables

Old text:

~~The primary efficacy variable will be the clinical response at the TOC visit in the modified Intent to Treat (mITT; ie, ITT population plus a pre-therapy culture positive for a Gram-negative respiratory tract pathogen and an APACHE II score of ≥ 10) population. The mITT population will be the primary analysis group.~~

~~Secondary efficacy variables will include CPIS changes through the TOC visit and comparisons (aerosolized BAY 41-6551 versus placebo) of the:~~

- ~~• number of days on mechanical ventilation through the Day 28 visit~~
- ~~• total number of days of Gram-negative IV antibiotics per patient~~
- ~~• number of ICU days at the Day 28 visit~~
- ~~• number of hospital days at the Day 28 visit~~
- ~~• clinical relapse rates at the Day 28 visit~~

~~Secondary microbiological objectives will include comparisons (aerosolized BAY 41-6551 versus placebo) of the:~~

- ~~• per pathogen microbiological response rates at the TOC visit~~
- ~~• per patient microbiological response rate at the TOC visit~~
- ~~• microbiological recurrence rates at the TOC and Day 28 visits~~
- ~~• emergence of new respiratory pathogens during the treatment period~~

- ~~emergence of resistance among baseline pathogens in those patients with persistent infection or colonization~~

New text:

9.6.1.1 Primary Efficacy Evaluation: Clinical Success

The primary efficacy evaluation is the Clinical Success, which is determined by using a computer algorithm based on collected data and specific criteria. For a patient to be evaluated as a Clinical Success, all the following criteria must be met:

- Systemic antibiotics (IV or PO) for pneumonia must be stopped on or before the TOC visit
- Systemic antibiotics (IV or PO) for pneumonia must not be restarted after the TOC visit
- The patient must survive through the LFU visit
- The patient must not have a reported AE of lung abscess or empyema through the LFU visit
- The patient must have stable respiratory function evaluated at the TOC visit based on the P/F ratio (See Section 8.2)

9.6.1.2 Investigator Assessment of Patient Outcome

The investigators will also assess patient outcome based on a composite endpoint. The Investigator Assessment of Patient Outcome is separate and different from the primary endpoint of Clinical Success, which is done by using a computer algorithm based on collected data and specific criteria. The Investigator Assessment of Patient Outcome is based on the following criteria:

- CPIS assessed at baseline, Days 3, 5, 10, and the TOC visit
- All-cause mortality assessed through the TOC visit
- Systemic antibacterial use for the current episode of pneumonia beyond Day 10 (the EOT for aerosol administration)
- Antibiotic adjustments made during therapy

Old text:

~~9.6.2.2 Clinical Response Assessments~~

~~9.6.2.2.1 End of Therapy (EOT) (Day 10)~~

~~At the EOT visit, the investigators or the sub-investigators will evaluate the patient's clinical response using the following terms and definition:~~

~~Clinical Cure:~~

~~....~~

- ~~The patient never reached any of the early failure criteria in Section 9.6.1.1; AND~~

....

NOTE: All four conditions listed above must be met in order for the ~~patient to be considered a Clinical Cure.~~

Clinical Failure

....

NOTE: ~~At least~~ one of the above conditions is ~~necessary to consider a patient a~~ **Clinical Failure.**

....

New text:

9.6.1.2.1 End of Therapy (EOT) (Day 10)

The Investigator Assessment of Patient Outcome will be evaluated at the EOT visit using the following terms and definition.

Investigator Assessment of Patient Outcome - Cure:

....

- The patient never reached any of the early failure criteria; AND
- The patient survived through the EOT visit

....

NOTE: All four conditions listed above must be met in order for the Investigator Assessment of Patient Outcome to be a cure.

Investigator Assessment of Patient Outcome - Failure:

....

- All-cause mortality by the EOT visit.

NOTE: If any one of the above conditions is met, the Investigator Assessment of Patient Outcome is a failure.

Old text:

9.6.2.2.2 Test-of-Cure (TOC) Visit (Day 17-19)

At the TOC visit, the investigator and/or sub-investigator(s) will evaluate the patient's clinical response using the following terms and definitions:

Clinical Cure:

....

NOTE: All five conditions listed above must be met in order for the ~~patient to be considered a Clinical Cure.~~

Clinical Failure:

....

NOTE: ~~At least~~ one of the above conditions is ~~necessary to consider~~ a patient a Clinical Failure.

....

At Day 10, corresponding to the completion of 20 doses (EOT), ~~Clinical Failure~~ will be defined as a failure to decrease the CPIS by 2 points. There may be instances at Day 10 where, if the CPIS falls by more than 2 points, there could still be reasons to continue IV antibiotic therapy and also instances where the score could fail to fall by more than 2 points and antibiotic therapy might be discontinued. In both instances of such ~~Clinical Failure~~, the reasons for continuing or discontinuing antibiotic therapy will be specified in the CRF.

~~Clinical failures~~ will be carried through the LFU visit evaluation

New text:

9.6.1.2.2 Test-of-Cure (TOC) Visit (Day 17-19)

The Investigator Assessment of Patient Outcome will be evaluated at the TOC visit using the following terms and definitions:

Investigator Assessment of Patient Outcome - Cure:

....

NOTE: All five conditions listed above must be met in order for the Investigator Assessment of Patient Outcome to be a cure.

Investigator Assessment of Patient Outcome - Failure:

....

- All cause mortality by the TOC visit

NOTE: If any one of the above conditions is met, the Investigator Assessment of Patient Outcome is a failure.

....

At Day 10, corresponding to the completion of 20 doses (EOT), patient outcome of failure will be defined as a failure to decrease the CPIS by 2 points. There may be instances at Day 10 where, if the CPIS falls by more than 2 points, there could still be reasons to continue IV antibiotic therapy and also instances where the score could fail to fall by more than 2 points and antibiotic therapy might be discontinued. In both instances of such patient outcome failure, the reasons for continuing or discontinuing antibiotic therapy will be specified in the CRF.

A patient outcome of failure will be carried through the LFU visit evaluation.

Old text:

9.6.2.2.3 Late Follow-up Visit (Days 28 - 32)

At the LFU visit, the investigator and/or sub-investigator(s) will evaluate the patient's clinical response. As mentioned previously, a patient evaluated at the TOC visit as a ~~Clinical Failure~~ will have that ~~clinical~~ response carried forward to the LFU visit.

For patients who were evaluated at the TOC visit as a ~~Clinical Cure~~, their clinical response will be graded as:

Continued ~~Clinical~~ Cure:

New text:

9.6.1.2.3 Late Follow-up Visit (Days 28 – 32)

The Investigator Assessment of Patient Outcome will be evaluated at the LFU visit. As mentioned previously, a patient evaluated at the TOC visit as a patient outcome failure will have that response carried forward to the LFU visit.

For patients who were evaluated at the TOC visit as a patient outcome cure, their clinical response will be graded as:

Continued Investigator Assessment of Patient Outcome Cure:...

Old text:

9.6.2.2.4 Premature Discontinuation Visit

....

~~In the case of a patient who is evaluated as a Clinical Failure~~ (ie, study drug therapy is discontinued because of a lack of therapeutic effect), the evaluation of their clinical condition should be based on the clinical signs and symptoms of pneumonia as well as objective evidence of failure (eg, persistent fever, rising WBC count, increasing tracheal secretions, poor oxygenation, progression of infiltrate on CXR) and a measure of their CPIS. This information should be recorded on the CRF, as well as an evaluation of the patient's clinical response to study drug. In most cases, the decision to evaluate the patient as a Clinical Failure will be made after at least 72 hours of study medication, but in rare instances, the clinical course of the illness may require that study medication be discontinued prior to three days treatment and alternative antibiotic therapy started. Regardless of when the patient is prematurely discontinued, the clinical condition of the patient should be determined at the time of study drug discontinuation, recorded on the CRF, and a clinical response evaluation completed.

At the premature discontinuation visit, the investigator and/or sub-investigator should evaluate the patient's ~~clinical response~~ according to the following terms and definitions.

Clinical Failure:

....

- Any further change to the antimicrobial regimen being used to treat pneumonia during the first 10 days, after the initial antimicrobial adjustment within the first 72 hours after the initiation of empiric therapy or as soon as initial culture and susceptibility results are available and excepting the discontinuation of aminoglycosides after 5-7 days, would be considered a ~~Clinical Failure~~;

....

~~NOTE: At least one of the above conditions is necessary to consider a patient a Clinical Failure.~~

....

~~At the premature discontinuation visit, the investigator and/or sub-investigator(s) will evaluate the patient's clinical response.~~

....

New text:

9.6.1.2.4 Premature Discontinuation Visit

....

For a patient outcome failure (ie, study drug therapy is discontinued because of a lack of therapeutic effect), the evaluation of the patient's clinical condition should be based on the clinical signs and symptoms of pneumonia as well as objective evidence of failure (eg, persistent fever, rising WBC count, increasing tracheal secretions, poor oxygenation, progression of infiltrate on CXR) and a measure of their CPIS. This information should be recorded on the CRF, as well as an evaluation of the patient's clinical response to study drug. In most cases, the decision to evaluate the patient as a Clinical Failure will be made after at least 72 hours of study medication, but in rare instances, the clinical course of the illness may require that study medication be discontinued prior to three days treatment and alternative antibiotic therapy started. Regardless of when the patient is prematurely discontinued, the clinical condition of the patient should be determined at the time of study drug discontinuation, recorded on the CRF, and a clinical response evaluation completed.

At the premature discontinuation visit, the patient's outcome response will be assessed according to the following terms and definitions.

Investigator Assessment of Patient Outcome - Failure:

....

- Any further change to the antimicrobial regimen being used to treat pneumonia during the first 10 days, after the initial antimicrobial adjustment within the first 72 hours after the initiation of empiric therapy or as soon as initial culture and susceptibility results are available and excepting the discontinuation of aminoglycosides after 5-7 days, would be considered a patient outcome failure;

....

NOTE: At least one of the above conditions is necessary to consider a patient a patient outcome failure.

11.1.1 Analysis Populations

Added text:

The two populations used for analysis will be the mITT population and the ITT population. These populations will be comprised of patients recruited to this study and to study 13085 (being conducted in different countries; the protocols are identical with the exception that study 13085 has a pharmacokinetic substudy). The patients will be recruited competitively between studies 13084 and 13085; there are no minimum requirements for recruitment totals in either study. The mITT population is defined as all randomized patients with culture-confirmed Gram-negative bacteria who have been treated with at least one dose of study drug and have an APACHE II score ≥ 10 at the time of diagnosis of pneumonia. The ITT population is defined as all patients treated with at least one dose of study drug.

11.1.2 Analytical Plan

Old text:

The primary efficacy analysis will be conducted in the mITT population. ~~Supportive efficacy analyses will be provided for the ITT population.~~ Unless otherwise specified, all significance tests will be conducted using a two-sided alpha level of 0.05

New text:

The primary efficacy analysis will be conducted in the mITT population. The primary analysis is on the combined database, no single study analyses will be performed as part of the primary analysis. Unless otherwise specified, all significance tests will be conducted using a two-sided alpha level of 0.05.

11.2 Determination of Sample Size

Old text:

For this study, a sample size of ~~215~~ patients per treatment group will provide 85% power to obtain a statistically significant result at a two-sided alpha level of 0.05, assuming true ~~clinical cure~~ rates at ~~TOC~~ of 55% for placebo and 69% for BAY 41-6551. Assuming 35% of patients will not be eligible for the primary efficacy analysis (ie, will not have a pre-therapy Gram-negative organism) a total of ~~334~~ patients per group (~~662~~ overall) will be needed for the study, based on current surveillance. If the actual rate of ineligible patients is different than 35%, the overall enrollment will be adjusted to ensure that ~~430~~ patients with Gram-negative organisms are enrolled. Note that with this sample size, an observed treatment group difference of as low as ~~9.3~~% could provide a statistically significant result.

New text:

For this combined study (studies 13084 and 13085), a sample size of 236 mITT patients per treatment group will provide 92% power to obtain a statistically significant result at a two-sided alpha level of 0.05, assuming true Clinical Success rates at LFU of 54% for placebo and 69% for BAY 41-6551. Assuming 35% of patients will not be eligible for the primary efficacy analysis (ie, will not have a pre-therapy Gram-negative organism) a total of 362 ITT patients per group (724 ITT overall) will be needed for the study, based on current surveillance. If the actual rate of ineligible patients is different than 35%, the overall enrollment will be adjusted to ensure that 472 patients with Gram-negative organisms are enrolled. Note that with this sample size, an observed treatment group difference of as low as 8.9% could provide a statistically significant result.

11.3 Methods for the Analysis of the Primary Efficacy Parameter

Old text:

The primary efficacy variable is clinical ~~response at the TOC visit~~. The primary analysis will compare the proportion of patients with ~~cures~~ in the BAY 41-6551 group versus the proportion in the placebo group. All assessments other than ~~cure~~ - failures, improvements, indeterminates, and missings (those patients who do not have a test of cure assessment) will be grouped together in a ~~non-cure~~ category for the purposes of this analysis.

The null (H_0) and the alternative (H_1) hypothesis for this primary analysis is the following:

- $H_0: p[\text{BAY 41-6551}] = p[\text{placebo}]$
- $H_1: p[\text{BAY 41-6551}] \neq p[\text{placebo}]$

where p is the true ~~cure~~ rate.

A Cochran-Mantel-Haenzel test of general association, adjusting for stratum and geographic region, will be performed as the primary efficacy analysis. If the p-value from this test is less than 0.05, and the proportion of patients with ~~cures~~ is higher in the BAY 41-6551 group than in the placebo group, the study will have achieved its primary objective.

In addition, as a supportive analysis, a 95% confidence interval will be calculated for the odds ratio. This confidence interval will be generated from a logistic regression model with

clinical response as the primary variable, and treatment, stratum, and geographic region as the independent variables. If the lower limit of the 95% confidence interval for the odds ratio (BAY 41-6551/placebo) is greater than 1, BAY 41-6551 will be demonstrated to be statistically superior to placebo.

....

The Breslow-Day test will be used as a further supportive analysis to test for treatment by geographic region and treatment by stratum interaction. If this test of the homogeneity of the odds ratio indicates a significant interaction, exploratory analyses will attempt to define its source.

....

In addition, an analysis of clinical response will be conducted that excludes patients who received anti-microbial therapy considered to be effective against Gram-negative organisms, for infections other than the underlying pneumonia. Patients will only be excluded from this analysis if the additional anti-microbial therapy was administered before the TOC visit and the patient was not a Clinical Failure.

...

New text:

The primary efficacy variable is Clinical Success. Clinical Success is achieved when all of the following criteria are met:

- 1) Systemic antibiotics (IV or PO) for pneumonia must be stopped on or before the TOC visit
- 2) Systemic antibiotics (IV or PO) for pneumonia must not be restarted after the TOC visit
- 3) The patient must survive through the LFU visit
- 4) The patient must not have a reported AE of lung abscess or empyema through the LFU visit
- 5) The patient must have stable respiratory function evaluated at the TOC visit based on the P/F ratio as outline below (if the P/F ratio is not available at the TOC, use the P/F ratio value from the closest previous visit):

Stable respiratory function

- Patient is extubated at the TOC visit OR
- Patient is intubated at the TOC visit AND:
 - Patient has a P/F ratio > 200 at the TOC visit OR
 - Patient has a P/F ratio > 100 and ≤ 200 at the TOC visit AND:
 - Patient had a P/F ratio ≤ 200 at baseline

Unstable respiratory function

- Patient has a P/F ratio ≤ 100 at the TOC visit OR

- Patient has a P/F ratio > 100 and ≤ 200 at the TOC visit AND:
 - Patient had a P/F ratio > 200 at baseline

The outcome is Clinical Success if all 5 criteria are met. If any one of the criteria is not met, then the patient is considered a Clinical Failure. Patients who do not have a clinical assessment of success due to missing data will be considered a Clinical Failure.

Patients who are discontinued from aerosol therapy will be evaluated as follows:

<u>Reason for Discontinuation of Aerosol Therapy</u>	<u>Outcome/Comments</u>
• <u>No Gram-negative bacteria isolated from a pre-therapy respiratory specimen</u>	• <u>Patient is considered ITT and not evaluated for efficacy</u>
• <u>Patient withdrew consent or refused handheld device</u>	• <u>Evaluate for efficacy if all data are available; if data are missing, then failure</u>
• <u>Death</u>	• <u>Failure</u>
• <u>Adverse event, abnormal laboratory value (elevated creatine, etc)</u>	• <u>Failure</u>
• <u>New therapy incompatible with aerosol therapy</u>	• <u>Failure</u>
• <u>Discharged/lost to follow-up</u>	• <u>Failure</u>
• <u>Any other reason/unknown reason</u>	• <u>Failure</u>

The primary analysis will compare the proportion of patients with Clinical Success in the BAY 41-6551 group versus the proportion in the placebo group, using the combined data from studies 13084 and 13085. All assessments other than Clinical Success - failures, improvements, and missings (those patients who do not have a TOC assessment) will be grouped together in the Clinical Failure category for the purposes of this analysis.

The null (H_0) and the alternative (H_1) hypothesis for this primary analysis is the following:

- $H_0: p[\text{BAY 41-6551}] = p[\text{placebo}]$
- $H_1: p[\text{BAY 41-6551}] \neq p[\text{placebo}]$

where p is the true Clinical Success rate.

A Cochran-Mantel-Haenzel test of general association, adjusting for stratum and geographic region, will be performed as the primary efficacy analysis. If the p-value from this test is less than 0.05, and the proportion of patients with Clinical Success is higher in the BAY 41-6551 group than in the placebo group, the study will have achieved its primary objective.

In addition, as a supportive analysis, a 95% confidence interval will be calculated for the odds ratio. This confidence interval will be generated from a logistic regression model with Clinical Success as the primary variable, and treatment, stratum, and geographic region as the independent variables. If the lower limit of the 95% confidence interval for the odds ratio (BAY 41-6551/placebo) is greater than 1, BAY 41-6551 will be demonstrated to be statistically superior to placebo.

The individual components of the composite endpoint will be analyzed using Mantel-Haenszel adjusting for stratum and geographic region. This is to assess if the components are moving in the same general direction and which, if any, single component is driving the result.

....

The Breslow-Day test will be used as a further supportive analysis to test for treatment by geographic region and treatment by stratum interaction. If this test of the homogeneity of the odds ratio indicates a significant interaction, exploratory analyses will attempt to define its source. A Cochran-Mantel-Haenzel test of general association, adjusting for stratum and study protocol (ie, 13084 or 13085), will be performed to assess the effect of study protocol on the primary outcome Clinical Success. Geographic region will not be included in this model as the 2 studies were conducted in different regions.

....

In addition, an analysis of Clinical Success will be conducted that excludes patients who received anti-microbial therapy considered to be effective against Gram-negative organisms, for infections other than the underlying pneumonia. Patients will only be excluded from this analysis if the additional anti-microbial therapy was administered before the TOC visit and the patient was not a Clinical Failure.

11.4 Methods for the Analysis of Secondary Efficacy Parameters

Old text:

If the null hypothesis for the primary efficacy variable is rejected, a formal hypothesis testing scenario will be applied for 4 secondary efficacy variables. ~~These four are:~~

- the number of days on mechanical ventilation
- the number of days in the ICU
- ~~• the number of days in the hospital~~
- ~~• relapse rates~~

~~For the first three variables, the counting of the totals will begin on the first day of study drug therapy and continue through Day 28.~~

~~Holm's sequentially rejective testing procedure will be used for these four secondary endpoints. With this approach, the p-values from the tests of the four variables are ordered from lowest to highest. If the lowest p-value is > 0.0125 ($0.05/4$), none of the null hypotheses of treatment equality for these variables will be rejected, and no more comparisons will be performed. If the lowest p-value is ≤ 0.0125 , the null hypothesis for that variable will be rejected, and the next lowest p-value will then be compared to 0.0167 ($0.05/3$). The tests will continue until the first time at which the null hypothesis is not rejected; all null hypotheses from that point on are also not rejected.~~

Analysis of variance will be used to test the null hypothesis of no difference between BAY 41-6551 and placebo for the ~~three secondary variables counting number of days in the sequentially rejective testing approach~~. For the purpose of the sequentially rejective testing procedure, the only effect in the model will be treatment ~~and the p-values from the treatment effect will be used to compare to the Holm boundaries~~. The null hypothesis of no difference between BAY 41-6551 and placebo in clinical relapse rates will be tested using an unadjusted Chi-square test.

As supportive analyses, additional models will be used with effects included for geographic region for all ~~four of these~~ secondary variables. Non-parametric tests for treatment comparisons will be considered as sensitivity analyses.

Analysis of variance will be used to test the null hypothesis of no difference between BAY 41-6551 and placebo for the total number of days of Gram-negative antibiotics.

The ~~remaining secondary~~ endpoints –total number of days of Gram-negative antibiotics, clinical response rates at end of therapy, change in component of CPIS score from baseline to TOC, and microbiological eradication rates, will be summarized descriptively. In addition, Kaplan-Meier curves will be provided for time to Clinical Failure.

New text:

If the null hypothesis for the primary efficacy variable is rejected, a formal hypothesis testing scenario will be applied for the secondary efficacy variables:

- Pneumonia-related mortality through the LFU visit
- Early Clinical Response (based on CPIS, mortality, and certain AEs) assessed through Day 10
- The number of days on mechanical ventilation through the LFU visit
- The number of days in the ICU through the LFU visit

The secondary efficacy variables will be formally tested for statistical significance of a difference between the BAY 41-6551 group versus the placebo group, only if the primary efficacy comparison is statistically significant at the two-sided 5% level. A sequential testing procedure will be performed at the two-sided alpha level of 0.05 for these four secondary efficacy variables, strictly in the order listed above.

The null hypothesis of no difference between BAY 41-6551 and placebo in pneumonia – related mortality and early clinical response will be tested using an unadjusted Chi-square test. Analysis of variance will be used to test the null hypothesis of no difference between BAY 41-6551 and placebo for the number of days on mechanical ventilation and in the ICU.

For the purpose of the sequentially rejective testing procedure, the only effect in the model will be treatment. As supportive analyses, additional models will be used with effects included for geographic region for all secondary variables. Non-parametric tests for treatment comparisons will be considered as sensitivity analyses.

The other endpoints – total number of days of Gram-negative antibiotics, clinical response rates at end of therapy, change in component of CPIS score from baseline to TOC,

microbiological eradication rates, the number of days in the hospital, and relapse rates will be summarized descriptively, however for the total number of days of Gram-negative antibiotics, analysis of variance will be used to test the null hypothesis of no difference between BAY 41-6551 and placebo. In addition, Kaplan-Meier curves will be provided for time to Clinical Failure. The Investigator Assessment of Patient Outcome will be analyzed as sensitivity analysis.

14. References

Old text:

41. Investigator's Brochure, Amikacin Pulmonary Delivery System; Version 3.0:
~~23-Apr-2014.~~

New text:

41. Investigator's Brochure, Amikacin Pulmonary Delivery System; Version 4.0:
19 FEB 2015.
49. The ARDS Definition Task Force. Acute respiratory distress syndrome. The Berlin definition. JAMA 2012;307(23):2526-33.

15.1. Study Flow Chart and Schedule of Procedures

Old text:

Assessment	Screening	Day										Premature D/C/Early Withdrawal	TOC Day 17 to 19	Late Follow-Up Day 28 to 32 ^b		
		1	2	3	4	5	6	7	8	9	10 ^a EOT			In Person	By Phone	
															
Arterial blood gases/pulse oximetry	X	X		X		X		X			X	X	X	X ^r		
....																
APACHE II score [†]	X															
....																
Collection of ventilator parameters pre- and post-dose		X	X	X	X	X	X	X	X	X						
....																
Evaluation of Clinical Response											X	X	X	X	X	
....																

l - APACHE II score for the 24 hours immediately preceding the first dose of study medication

....

n - Prior to each dose, each patient will receive a carton containing one vial of study medication (either BAY 41-6551 or placebo) and one nebulizer/reservoir.

o - Patients will be started on aerosolized study medication within 24 hours of systemic antibiotic therapy being initiated. Patients will receive 3.2 mL of either BAY 41-6551 (400 mg, amikacin as free base) or placebo solution every 12 hours via the PDDS Clinical for ten days (20 doses). If a patient is extubated during the course of treatment or has had a tracheostomy and is spontaneously breathing, aerosol administration will continue via the handheld adaptor for the remainder of the treatment period.

p - Serum amikacin for trough level will be obtained 30 minutes prior to the first dose on each treatment day. In addition, these trough levels should be obtained for all patients and be sent to the Central Laboratory. If the site has mandated procedures for monitoring IV amikacin treatment, the site should perform these site-specific procedures in conjunction with the collection for serum Amikacin levels.

....

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New text:

Assessment	Screening	Day										Premature D/C/Early Withdrawal	TOC Day 17 to 19	Late Follow-Up Day 28 to 32 ^b			
		1	2	3	4	5	6	7	8	9	10 ^a EOT			In Person	By Phone		
....																	
Arterial blood gases/pulse oximetry	X	X		X		X		X				X	X ^s	X ^s	X ^r		
....																	
APACHE II score	X																
....																	
Collection of ventilator parameters pre- and post-dose		X	X	X	X	X	X	X	X	X	X	X					
....																	
<u>Investigator Assessment of Patient Outcome</u>												X	X	X	X	X	X
....																	

....
l – Footnote deleted per Amendment 6.

....
n - Prior to each dose, each patient will receive a one vial of study medication (either BAY 41-6551 or placebo) and one nebulizer/reservoir.

o - Patients will be started on aerosolized study medication within 48 hours of systemic antibiotic therapy being initiated. Patients will receive 3.2 mL of either BAY 41-6551 (400 mg, amikacin as free base) or placebo every 12 hours via the PDDS Clinical for ten days (20 doses). If a patient is extubated during the course of treatment or has had a tracheostomy and is spontaneously breathing, aerosol administration will continue via the handheld adaptor for the remainder of the treatment period.

p - Serum amikacin for trough level will be obtained 30 ± 15 minutes prior to the first dose on each treatment day. In addition, these trough levels should be obtained for all patients and be sent to the Central Laboratory. If the site has mandated procedures for monitoring IV amikacin treatment, the site should perform these site-specific procedures in conjunction with the collection for serum Amikacin levels.

....
s – Pulse oximetry not required at the premature discontinuation/early withdrawal and TOC visits.

15.3. Clinical Pulmonary Infection Score (CPIS)

Old text:

CPIS Points	0	1	2
Tracheal secretions	Few (purulent + 1)	Moderate (purulent + 1)	Large (purulent + 1)
Chest radiograph	No infiltrate	Patchy or Diffuse	Localized
Temperature (core), °C	≥ 36.5 and ≤ 38.4	≥ 38.5 and ≤ 38.9	≥ 39.0 or ≤ 36.0
Blood leukocytes, per mm ³	≥ 4,000 and ≤ 11,000	< 4,000 or > 11,000	--
Oxygenation PaO ₂ / FiO ₂ , mm Hg	> 240 or presence of ARDS	--	≤ 240 and absence of ARDS

ARDS – acute respiratory distress syndrome

~~*CPIS for Screening/Randomization purposes is calculated from the 5 components.~~

Guidance for Investigators for Calculating the CPIS

- **Tracheal secretions:** to assign a point score for the quantity and appearance of tracheal secretions observed in the last 24 hours, consult the nursing/respiratory therapy notes for the best estimate
 - Add 1 point, if the tracheal secretions are considered purulent (e.g., if the patient had “few” secretions but they were purulent, then the patient would have a score of 1 for this component of the score; or if the patient had a “large” amount of purulent secretions, then the score would be 3)
- **Chest radiograph (CXR):** the CXR taken within the previous 24 h (or sooner)
- **Temperature, °C:** the maximal temperature taken within the previous 24 hours should be used for point assignment
 - For patients with hypothermia, the lowest temperature taken in the previous 24 hours should be used for point assignment
- **Blood leukocytes (WBC) (cells/mm³):** the maximal WBC count reported in the previous 24 hours should be used for point assignment
 - For patients with leukopenia, the lowest WBC count reported in the previous 24 hours should be used for point assignment
- **Oxygenation PaO₂ / FiO₂, mm Hg:** the most recently calculated P/F ratio obtained within the last 24 hours should be used for point assignment

New text:

CPIS Points	0	1	2
Tracheal secretions	Few (purulent + 1)	Moderate (purulent + 1)	Large (purulent + 1)
Chest radiograph	No infiltrate	Patchy or Diffuse	Localized
Temperature (core), °C	≥ 36.1 and ≤ 38.4	≥ 38.5 and ≤ 38.9	≥ 39.0 or ≤ 36.0
Blood leukocytes, per mm ³	≥ 4,000 and ≤ 11,000	< 4,000 or > 11,000	--
Oxygenation PaO ₂ / FiO ₂ , mm Hg	> 240 or presence of ARDS	--	≤ 240 and absence of ARDS

ARDS – acute respiratory distress syndrome

Guidance for Investigators for Calculating the CPIS

- **Tracheal secretions:** to assign a point score for the quantity and appearance of tracheal secretions observed in the last 24 hours⁹⁷, consult the nursing/respiratory therapy notes for the best estimate
 - Add 1 point, if the tracheal secretions are considered purulent (e.g., if the patient had “few” secretions but they were purulent, then the patient would have a score of 1 for this component of the score; or if the patient had a “large” amount of purulent secretions, then the score would be 3)
- **Chest radiograph (CXR):** the most recent CXR taken within the previous 24 hours⁹⁷ (or sooner)
- **Temperature, °C:** the maximal temperature taken within the previous 24 hours⁹⁷ should be used for point assignment
 - For patients with hypothermia, the lowest temperature taken in the previous 24 hours⁹⁷ should be used for point assignment
- **Blood leukocytes (WBC) (cells/mm³):** the maximal WBC count reported in the previous 24 hours⁹⁷ should be used for point assignment
 - For patients with leukopenia, the lowest WBC count reported in the previous 24 hours⁹⁷ should be used for point assignment
- **Oxygenation PaO₂ / FiO₂, mm Hg:** the most recently calculated P/F ratio obtained within the last 24 hours⁹⁷ should be used for point assignment

⁹⁷within 48 hours for the screening visit; within 24 hours for all other visits

15.5. APACHE II Score / Glasgow Score

Old text:

....

~~During the first 24 hours after admission, the point score is calculated from 12 routine physiological measurements (such as blood pressure, body temperature, heart rate etc.) during the first 24 hours after admission, information about previous health status and other information obtained at admission (such as age). The calculation method is optimized for paper schemas. The resulting point score should always be interpreted in relation to the illness of the patient.~~

After the initial APACHE II score has been determined, no new score can be ~~calculated~~ during the hospital stay. If a patient is discharged from the ICU and readmitted, a new APACHE II score can be calculated.

....

New text:

....

The point score is calculated from 12 routine physiological measurements (such as blood pressure, body temperature, heart rate etc.). The calculation method is optimized for paper schemas. The resulting point score should always be interpreted in relation to the illness of the patient.

After the initial APACHE II score has been determined, no new score can be entered for this study during the hospital stay. If a patient is discharged from the ICU and readmitted, a new APACHE II score can be calculated.

....

Added text:

Glasgow Coma Scale		B	Age	Point	C	Chronic Health Points	APACHE II Score
Eyes open	Verbal – non-intubated	Age		Points			(sum of A + B + C) A APS points
4 - spontaneously	5 - oriented and conversant	< 44		0		If any of the 5 CHE categories is answered with yes give +5 points for non-operative or emergency postoperative patients <u>with immunocompromised or severe organ insufficiency</u> <u>+2 points for elective postoperative patient with immunocompromised or history of severe organ insufficiency</u>	+ B Age points
3 - to verbal	4 - disoriented and talks	45-54		2	Liver	- Cirrhosis with PHT or encephalopathy	+ C Chronic Health Points
2 - to painful stimuli	3 -inappropriate words	55-64		3	Cardiovascular	- class IV angina or at rest or with minimal self care activities - chronic hypoxemia or hypercapnia or polycytaemia of PHT > 40mmHg	_____
1 - no response	2 -incomprehensible sounds	65-74		5	Pulmonary	- chronic peritoneal or haemodialysis	= Total APACHE II
Motor response	Verbal - intubated	> 75		6	Kidney	- immune compromised host	
6 - to verbal command	5 -seems able to talk				Immune		
5 - localizes to pain	3 -questionable ability to talk 1 -generally unresponsive	Age points =				Chronic Health Points =	
4 - withdraws to pain							
3 - decorticate							
2 - decerebrate							
1 - no response							

16.7 Amendment 7

16.7.1 Overview of Change

A correction has been made in the temperature criterion for the calculation of CPIS points. This correction accurately reflects the programming that has been used in the eCRF by the investigators to calculate the CPIS score throughout the study, ie, it does not represent a change in the conduct of the study.

16.7.2 Changes to the Protocol Text

In this section, deleted text is ~~crossed out~~ and added text is underlined.

15.3. Clinical Pulmonary Infection Score (CPIS)

Old text:

CPIS Points	0	1	2
Tracheal secretions	Few (purulent + 1)	Moderate (purulent + 1)	Large (purulent + 1)
Chest radiograph	No infiltrate	Patchy or Diffuse	Localized
Temperature (core), °C	≥ 36.4 and ≤ 38.4	≥ 38.5 and ≤ 38.9	≥ 39.0 or ≤ 36.0
Blood leukocytes, per mm ³	≥ 4,000 and ≤ 11,000	< 4,000 or > 11,000	--
Oxygenation PaO ₂ / FiO ₂ , mm Hg	> 240 or presence of ARDS	--	≤ 240 and absence of ARDS

ARDS – acute respiratory distress syndrome

New text:

CPIS Points	0	1	2
Tracheal secretions	Few (purulent + 1)	Moderate (purulent + 1)	Large (purulent + 1)
Chest radiograph	No infiltrate	Patchy or Diffuse	Localized
Temperature (core), °C	≥ <u>36.5</u> and ≤ 38.4	≥ 38.5 and ≤ 38.9	≥ 39.0 or ≤ <u>36.4</u>
Blood leukocytes, per mm ³	≥ 4,000 and ≤ 11,000	< 4,000 or > 11,000	--
Oxygenation PaO ₂ / FiO ₂ , mm Hg	> 240 or presence of ARDS	--	≤ 240 and absence of ARDS

ARDS – acute respiratory distress syndrome

16.8 Amendment 8

This is a global amendment to Protocol 13084, Version 8.0 (dated 30 AUG 2016), and will be included as part of the integrated global protocol.

Minor changes to the protocol include editorial changes, correction of typographical errors, and minor revisions of language to ensure clarity and consistency throughout the document.

16.8.1 Overview of Change

This section provides a conceptual overview of all modifications to the original protocol Version 8.0, as introduced by this amendment. The associated changes to the protocol text are detailed in Section 16.8.2.

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 occasioned by the antibiotic duration 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 will be the sole criteria for evaluation.

The changes to the protocol are summarized below:

- The primary efficacy endpoint has been modified to all-cause mortality through the LFU visit.
- Name of sponsor's medical responsible persons
- The Signature of the sponsor's medically responsible persons, Synopsis, and Sections 5.1, 6, 8.1, 8.2, 8.4.1.1.4, 9.6.1.1, 9.6.1.2, 11.2, 11.3, 11.4, 11.5 and 15.1 were revised.

16.8.2 Changes to the Protocol Text

In this section, all sections affected by this amendment are detailed; the sequence follows the structure of the most recent previous protocol version. ~~Deletions are crossed out~~ and additions are underlined. Minor editorial changes and corrections of typographical errors are not shown.

Signature of the sponsor's medically responsible persons

Old Text

Name: PPD

Role: PPD

Signature:

Date:

Name: PPD

Role: PPD

Signature:

Date:



New Text

Name: PPD

Role: PPD

Signature: _____

Date: _____

Synopsis

Old Text

Diagnosis and main criteria for inclusion/exclusion	Patients of age 18 and older, who are hospitalized, have pneumonia suspected or confirmed to be caused by Gram-negative organisms, and who are intubated and mechanically-ventilated will be selected for this study. In all patients where the pathogen is suspected of being Gram-negative, it should be confirmed as soon as culture results are available. Patients with microbiologically-confirmed pneumonia are those who have a Gram-negative organism cultured from an appropriate respiratory tract specimen collected prior to enrollment . The main inclusion criteria are:
--	--

New Text

Diagnosis and main criteria for inclusion/exclusion	Patients of age 18 and older, who are hospitalized, have pneumonia suspected or confirmed to be caused by Gram-negative organisms, and who are intubated and mechanically-ventilated will be selected for this study. In all patients where the pathogen is suspected of being Gram-negative, it should be confirmed as soon as culture results are available. Patients with microbiologically-confirmed pneumonia are those who have a Gram-negative organism cultured from an appropriate respiratory tract specimen. The main inclusion criteria are:
--	--

Old Text

Study objectives	The study objective is to demonstrate that as adjunctive therapy to (intravenous) 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. The efficacy endpoint is Clinical Success as defined in Section 8.2. The secondary endpoint objectives are to evaluate the superiority of aerosolized BAY 41-6551 versus aerosolized placebo in pneumonia-related mortality, the Early Clinical Response at Day 10, the days on ventilation, and the days in the ICU.
-------------------------	---

New Text

Study objectives	The study objective is to demonstrate that as adjunctive therapy to (intravenous) 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. The <u>primary efficacy variable</u> is <u>Survival</u> as defined in Section 8.2. The secondary objectives are to evaluate the superiority of aerosolized BAY 41-6551 versus aerosolized placebo in pneumonia-related mortality, the Early Clinical Response at Day 10, the days on ventilation, and the days in the ICU.
-------------------------	--

Old text:

Safety endpoints	The safety endpoints are to compare (BAY 41-6551 vs aerosolized placebo, as adjunctive therapy to IV antibiotics in both arms) as measured by: <ul style="list-style-type: none"> • The frequency of adverse events (AEs) • The progression and incidence rates of organ failure • The all-cause mortality rate during therapy, at Day 15 and at Day 28
-------------------------	--

New text

Safety endpoints	The safety endpoints are to compare (BAY 41-6551 vs aerosolized placebo, as adjunctive therapy to IV antibiotics in both arms) as measured by: <ul style="list-style-type: none"> • The frequency of adverse events (AEs) • The progression and incidence rates of organ failure • The all-cause mortality rate during therapy, at Day 15 and at Day 28 (<u>also the primary efficacy endpoint</u>)
-------------------------	--

Old Text

Methodology	Eighteen to 22 days after completing 10 days of aerosolized treatment, patients will be evaluated for Clinical Success, which will be based on survival, the duration of antibiotic therapy, the absence of empyema or lung abscess, and stable respiratory function.
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New Text

Methodology	Eighteen to 22 days after completing 10 days of aerosolized treatment, patients will be evaluated for <u>Survival. Patients who survive through the late follow up visit are considered a success, patients who suffer mortality for any reason on or before the LFU visit are considered a failure.</u>
--------------------	--

Old Text

<p>Efficacy variables</p>	<p>The primary efficacy variable will be Clinical Success in the mITT population (ie, the ITT population who prove to be culture positive for a Gram-negative pathogen and have an APACHE II score \geq 10). Clinical Success is achieved when all of the following criteria are met:</p> <ol style="list-style-type: none"> 1) Systemic antibiotics (IV or by mouth [PO]) for pneumonia must be stopped on or before the Test of Cure (TOC) visit (Day 17-19) 2) Systemic antibiotics (IV or PO) for pneumonia must not be restarted after the TOC visit 3) The patient must survive through the late follow up (LFU) visit 4) The patient must not have a reported AE of lung abscess or empyema through the LFU visit and 5) The patient must have stable respiratory function measured at the TOC visit. <p>• ...</p> <p>The investigator will assess patient signs and symptoms at the TOC visit (Day 17-19) for the Investigator Assessment of Patient Outcome, which is separate from the primary efficacy variable, Clinical Success.</p>
----------------------------------	--

New Text

<p>Efficacy variables</p>	<p>The primary efficacy variable will be <u>Survival</u> in the mITT population (ie, the ITT population who prove to be culture positive for a Gram-negative pathogen and have an APACHE II score \geq 10). <u>Survival</u> is achieved when <u>the patient is documented as alive through the LFU visit.</u></p> <p>...</p> <p><u>Three additional analysis of clinical success will be conducted.</u></p> <ul style="list-style-type: none"> • <u>Clinical success using Foundation for the National Institute of Health (FNIH) recommendations is defined as mITT patients who survived through the LFU visit and did not have septic shock.</u> • <u>Investigator Assessment of Patient Outcome will be determined at the TOC visit (Day17-19). The investigator will assess patient signs and symptoms at the TOC visit.</u> • <u>Clinical Success will be evaluated using 5 component criteria, which were the former primary end point for this study.</u>
----------------------------------	---

5.1 Background and Rationale – amended

Old Text

Old Text

Inhalation delivery of BAY 41-6551 (amikacin solution for inhalation) offers an attractive addition to IV or IM delivery. Inhalation administration minimizes systemic exposure while delivering drug directly to the site of infection. Bayer HealthCare is investigating the use of aerosolized BAY 41-6551 for the treatment of serious bacterial respiratory infections in intubated and mechanically-ventilated patients using a proprietary high efficiency Pulmonary Drug Delivery System (PDDS Clinical).

...

This clinical study will evaluate the ~~Clinical Success~~ rate of aerosolized amikacin, administered via PDDS Clinical, to that of aerosolized placebo (normal saline solution), as adjunctive therapy to IV antibiotics in both arms, in patients with microbiologically-confirmed Gram-negative pneumonia. The PDDS Clinical is expected to be a more efficient way of delivering aerosolized medication than a conventional pneumatic system. The study will also provide information on the safety and tolerability of aerosolized amikacin.

New Text

Inhalation delivery of BAY 41-6551 (amikacin solution for inhalation) offers an attractive addition to IV or IM delivery. Inhalation administration minimizes systemic exposure while delivering drug directly to the site of infection. Bayer is investigating the use of aerosolized BAY 41-6551 for the treatment of serious bacterial respiratory infections in intubated and mechanically-ventilated patients using a proprietary high efficiency Pulmonary Drug Delivery System (PDDS Clinical).

...

This clinical study will evaluate the Survival rate of patients treated with aerosolized amikacin, administered via PDDS Clinical, to that of aerosolized placebo (normal saline solution), as adjunctive therapy to IV antibiotics in both arms, in patients with microbiologically-confirmed Gram-negative pneumonia. The PDDS Clinical is expected to be a more efficient way of delivering aerosolized medication than a conventional pneumatic system. The study will also provide information on the safety and tolerability of aerosolized amikacin.

6. Study Objectives – amended

Old Text

The study objective is 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. The efficacy ~~endpoint~~ is ~~Clinical Success~~ as defined in Section 8.2. The secondary objectives are to evaluate the superiority of aerosolized BAY 41-6551 versus aerosolized placebo in pneumonia-related mortality to the LFU visit, the Early Clinical Response at Day 10, the days on ventilation through the LFU visit, and the days in the ICU assessed at the LFU visit.

New Text

The study objective is 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. The primary efficacy variable is Survival as defined in Section 8.2. The secondary objectives are to evaluate the superiority of aerosolized BAY 41-6551 versus aerosolized placebo in pneumonia-related mortality to the Late Follow-up (LFU) visit, the Early Clinical Response at Day 10, the days on ventilation through the LFU visit, and the days in the ICU assessed at the LFU visit.

8.1 Study Design – amended

Old Text

This is a Phase III, prospective, randomized, double-blind, placebo-controlled, multicenter, multinational study designed to show that aerosolized BAY 41-6551 400 mg (amikacin as free base) every 12 hours is more effective than placebo (aerosolized normal saline), as adjunctive therapy to IV antibiotics ~~in both arms~~, in intubated and mechanically-ventilated patients with Gram-negative pneumonia.

New Text

This is a Phase III, prospective, randomized, double-blind, placebo-controlled, multicenter, multinational study designed to show that aerosolized BAY 41-6551 400 mg (amikacin as free base) every 12 hours is more effective than placebo (aerosolized normal saline), as adjunctive therapy to IV antibiotics, in intubated and mechanically-ventilated patients with Gram-negative pneumonia.

8.2 Study Plan – amended

Old Text

The Test-of-Cure (TOC) visit will be conducted on Day 17-19 of the study. The late follow-up (LFU) visit will be conducted on Day 28-32 of the study. ~~Clinical Success~~ will be

evaluated at the TOC and LFU visits by programmed response criteria. If available, respiratory secretions will be obtained, cultured, and evaluated for the emergence of resistance to study drug therapy among baseline organisms.

The primary efficacy evaluation of the study is the Clinical Success in the mITT population; which is achieved when the following 5 criteria are met:

- Systemic antibiotics (IV or by mouth [PO]) for pneumonia must be stopped on or before the TOC visit
- Systemic antibiotics (IV or PO) for pneumonia must not be restarted after the TOC visit
- The patient must survive through the LFU visit
- The patient must not have a reported AE of lung abscess or empyema through the LFU visit
- The patient must have stable respiratory function at the TOC visit

Stable or unstable respiratory function is determined based on the PaO₂/FiO₂ (P/F) ratio at TOC in the following manner:

Stable respiratory function:

- Patient is extubated at the TOC visit OR
- Patient is intubated at the TOC visit AND:
 - Patient has a P/F ratio > 200 at the TOC visit OR
 - Patient has a P/F ratio > 100 and ≤ 200 at the TOC visit AND:
 - Patient had a P/F ratio ≤ 200 at baseline

Unstable respiratory function

- Patient has a P/F ratio ≤ 100 at the TOC visit OR
- Patient has a P/F ratio > 100 and ≤ 200 at the TOC visit AND:
 - Patient had a P/F ratio > 200 at baseline

The outcome is Clinical Success if all 5 criteria are met. If any one of the criteria is not met, then the patient is considered a Clinical Failure. Patients who do not have a clinical assessment of success due to missing data will be considered a Clinical Failure.

New Text

The Test-of-Cure (TOC) visit will be conducted on Day 17-19 of the study. The late follow-up (LFU) visit will be conducted on Day 28-32 of the study. Survival will be evaluated through the LFU visit. If available, respiratory secretions will be obtained, cultured, and evaluated for the emergence of resistance to study drug therapy among baseline organisms.

The primary efficacy variable of the study is Survival in the mITT population through the LFU visit.

Section 8.4.1.1.4 Adjustment of Empiric Intravenous Antibiotic Therapy - amended

Old Text

Further adjustments to maintenance antibiotic therapy are not permitted during the remaining treatment unless the patient is failing antibiotic treatment for pneumonia, in which case the patient would be considered a failure by the Investigator Assessment (not by the primary endpoint evaluation of ~~Clinical Success~~).

New Text

Further adjustments to maintenance antibiotic therapy are not permitted during the remaining treatment unless the patient is failing antibiotic treatment for pneumonia, in which case the patient would be considered a failure by the Investigator Assessment (not by the primary endpoint evaluation of Survival).

Section 8.4.2 Identity of Investigational Products

Old Text

The active ingredient will be obtained from ACS Dobfar (Bergamo, Italy) and the BAY 41-6551 inhalation solution will be manufactured by Bayer ~~HealthCare~~-AG (Leverkusen, Germany). Each single-use vial has a filling volume of 3.6 mL. This fill volume of 3.6 mL is equivalent to the BAY 41-6551 solution containing 450 mg of amikacin free base at a concentration of 125 mg/mL to ensure an extractable volume of 3.2 mL. The 3.2 mL extractable volume is equivalent to 400 mg amikacin free base aerosolized. BAY 41-6551 inhalation solution appears as a clear, colorless to slightly yellowish solution. Other excipients or components of the solution include: hydrochloric acid, sodium hydroxide, water for injection, and nitrogen.

New Text

The active ingredient will be obtained from ACS Dobfar (Bergamo, Italy) and the BAY 41-6551 inhalation solution will be manufactured by Bayer AG (Leverkusen, Germany). Each single-use vial has a filling volume of 3.6 mL. This fill volume of 3.6 mL is equivalent to the BAY 41-6551 solution containing 450 mg of amikacin free base at a concentration of 125 mg/mL to ensure an extractable volume of 3.2 mL. The 3.2 mL extractable volume is equivalent to 400 mg amikacin free base aerosolized. BAY 41-6551 inhalation solution appears as a clear, colorless to slightly yellowish solution. Other excipients or components of the solution include: hydrochloric acid, sodium hydroxide, water for injection, and nitrogen.

Section 9.6.1.1 Primary Efficacy Variable: Survival – amended

Old Text

Primary Efficacy Evaluation: ~~Clinical Success~~ - amended

The primary efficacy evaluation is the ~~Clinical Success~~, which is determined by ~~using a computer algorithm based on collected data and specific criteria. For a patient to be evaluated as a Clinical Success, all the following criteria must be met:~~

- ~~Systemic antibiotics (IV or PO) for pneumonia must be stopped on or before the TOC visit~~
- ~~Systemic antibiotics (IV or PO) for pneumonia must not be restarted after the TOC visit~~
- ~~The patient must survive through the LFU visit~~
- ~~The patient must not have a reported AE of lung abscess or empyema through the LFU visit~~
- ~~The patient must have stable respiratory function evaluated at the TOC visit based on the P/F ratio (see Section 8.2)~~

New Text

Primary Efficacy Variable: Survival - amended

The primary efficacy variable is Survival, which is determined by tabulating the cumulative mortality and survival through the LFU visit for each mITT patient. Survival (and mortality) is the only criteria evaluated for the primary endpoint, no other factors are considered other than survival status through the LFU visit.

Section 9.6.1.2 Additional Analysis of Clinical Success - amended

Added Text

9.6.1.2 Additional Analysis of Clinical Success - amended

There are three additional analyses of clinical success. These three analyses are separate from the primary endpoint. The three analyses are (1) the FNIH recommendations for an endpoint based on mortality plus septic shock, (2) the Investigator's assessment of Patient Outcome, and (3) the Composite Endpoint Evaluation (the previous Primary Endpoint).

9.1.6.2.1 FNIH Criteria - amended

Clinical success using FNIH recommendations is defined as mITT patients who survived through the LFU visit and did not have septic shock. Patients will be designated as having a septic shock event based on the standard medical queries (SMQ) terms tabulated as adverse events.

Section 9.6.1.2.2 Investigator Assessment of Patient Outcome - amended

Old Text

The investigators will also assess patient outcome based on a composite endpoint. The Investigator Assessment of Patient Outcome is separate and different from the primary endpoint of Clinical Success, which is done by using a computer algorithm based on collected data and specific criteria. The Investigator Assessment of Patient Outcome is based on the following criteria:

New Text

The investigators will also assess patient outcome based on a composite endpoint. The Investigator Assessment of Patient Outcome is separate and different from the primary endpoint of Survival, which is done by using a computer algorithm based on collected data and specific criteria. The Investigator Assessment of Patient Outcome is based on the following criteria:

9.6.1.2.3 Composite End Point Evaluation: - amended

Added Text

An evaluation of patient outcome based on 5 components is determined by using a computer algorithm based on collected data and specific criteria. This assessment based on 5 criteria is separate and different from the Primary End point of Survival. For a patient to be evaluated as a Clinical Success for the Composite End point Evaluation all the following criteria must be met:

- Systemic antibiotics (IV or PO) for pneumonia must be stopped on or before the TOC visit
- Systemic antibiotics (IV or PO) for pneumonia must not be restarted after the TOC visit
- The patient must survive through the LFU visit
- The patient must not have a reported AE of lung abscess or empyema through the LFU visit
- The patient must have stable respiratory function evaluated at the TOC visit based on the P/F ratio (see below)

Stable respiratory function:

- Patient is extubated at the TOC visit OR
- Patient is intubated at the TOC visit AND:
 - Patient has a P/F ratio > 200 at the TOC visit OR
 - Patient has a P/F ratio > 100 and ≤ 200 at the TOC visit AND:
 - Patient had a P/F ratio ≤ 200 at baseline

Unstable respiratory function

- Patient has a P/F ratio \leq 100 at the TOC visit OR
- Patient has a P/F ratio $>$ 100 and \leq 200 at the TOC visit AND:
 - Patient had a P/F ratio $>$ 200 at baseline

The outcome is Clinical Success if all 5 criteria are met. If any one of the criteria is not met, then the patient is considered a Clinical Failure. Patients who do not have a clinical assessment of success due to missing data will be considered a Clinical Failure.

9.6.2 Safety Variables

Old Text

Mortality during the treatment period, Day 15 and Day 28 visit will be summarized.

New Text

Mortality during the treatment period, Day 15 and Day 28 visit will be summarized (This is also the primary efficacy endpoint).

Section 11.2 Determination of Sample Size – amended

Old Text

~~For this combined study (studies 13084 and 13085), a sample size of 236 mITT patients per treatment group will provide 92% power to obtain a statistically significant result at a two-sided alpha level of 0.05, assuming true Clinical Success rates at LFU of 54% for placebo and 69% for BAY 41-6551. Assuming 35% of patients will not be eligible for the primary efficacy analysis (ie, will not have a pre-therapy Gram-negative organism) a total of 362 ITT patients per group (724 ITT overall) will be needed for the study, based on current surveillance. If the actual rate of ineligible patients is different than 35%, the overall enrollment will be adjusted to ensure that 472 patients with Gram-negative organisms are enrolled. Note that with this sample size, an observed treatment group difference of as low as 8.9% could provide a statistically significant result.~~

New Text

For this combined study (studies 13084 and 13085), a two group χ^2 test with a 0.05 two-sided significance level will have 81% power to detect the difference between BAY 41-6551 survival rate at LFU of 80% and Placebo survival rate at LFU of 69% when the sample size in each group is 254.

Assuming approximately 30% of patients will not be eligible for the primary efficacy analysis (ie, will not have a pre-therapy Gram-negative organism) a total of 362 ITT patients per group (724 ITT overall) will be needed for the study, based on current surveillance. Note that with this sample size, an observed treatment group difference of as low as 7.74% could provide a statistically significant result.

Section 11.3 Methods for the Analysis of the Primary Efficacy Parameter (Survival) – amended

Old Text

The primary efficacy variable is the ~~Clinical Success~~. ~~Clinical Success~~ is achieved when all of the following criteria are met:

- ~~1) Systemic antibiotics (IV or PO) for pneumonia must be stopped on or before the TOC visit~~
- ~~2) Systemic antibiotics (IV or PO) for pneumonia must not be restarted after the TOC visit~~
- ~~3) The patient must survive through the LFU visit~~
- ~~4) The patient must not have a reported AE of lung abscess or empyema through the LFU visit~~
- ~~5) The patient must have stable respiratory function evaluated at the TOC visit based on the P/F ratio as outline below (if the P/F ratio is not available at the TOC, use the P/F ratio value from the closest previous visit):~~

~~Stable respiratory function~~

- ~~• Patient is extubated at the TOC visit OR~~
- ~~• Patient is intubated at the TOC visit AND:~~
 - ~~○ Patient has a P/F ratio > 200 at the TOC visit OR~~
 - ~~○ Patient has a P/F ratio > 100 and ≤ 200 at the TOC visit AND:~~
 - ~~▪ Patient had a P/F ratio ≤ 200 at baseline~~

~~Unstable respiratory function~~

- ~~• Patient has a P/F ratio ≤ 100 at the TOC visit OR~~
- ~~• Patient has a P/F ratio > 100 and ≤ 200 at the TOC visit AND:~~
 - ~~○ Patient had a P/F ratio > 200 at baseline~~

The outcome is ~~Clinical Success~~ if all 5 criteria are met. If any one of the criteria is not met, then the patient is considered a ~~Clinical Failure~~. Patients who do not have a clinical assessment of success due to missing data will be considered a ~~Clinical Failure~~.

Patients who are discontinued from aerosol therapy will be evaluated as follows:

Reason for Discontinuation of Aerosol Therapy

- ~~No Gram negative bacteria isolated from a pre-therapy respiratory specimen~~
- ~~Patient withdrew consent or refused handheld device~~
- ~~Death~~
- ~~Adverse event, abnormal laboratory value (elevated creatine, etc)~~
- ~~New therapy incompatible with aerosol therapy~~
- ~~Discharged/lost to follow up~~
- ~~Any other reason/unknown reason~~

Outcome/Comments

- ~~Patient is considered ITT and not evaluated for efficacy~~
- ~~Evaluate for efficacy if all data are available; if data are missing, then failure~~
- ~~Failure~~
- ~~Failure~~
- ~~Failure~~
- ~~Failure~~
- ~~Failure~~

The primary analysis will compare the ~~proportion of patients with Clinical Success in the BAY 41-6551 group versus the proportion in the placebo group, using the combined data from studies 13084 and 13085. All assessments other than Clinical Success – failures, improvements, and missings (those patients who do not have a TOC assessment) will be grouped together in the Clinical Failure category for the purposes of this analysis.~~

The null (H_0) and the alternative (H_1) hypothesis for this primary analysis is the following:

- $H_0: p[\text{BAY 41-6551}] = p[\text{placebo}]$
- $H_1: p[\text{BAY 41-6551}] \neq p[\text{placebo}]$

where p is the true ~~Clinical Success~~ rate.

A Cochran-Mantel-Haenzel test of general association, adjusting for stratum and geographic region, will be performed as the primary efficacy analysis. If the p -value from this test is less than 0.05, and the proportion of patients ~~with Clinical Success~~ is higher in the BAY 41-6551 group than in the placebo group, the study will have achieved its primary objective.

In addition, as a supportive analysis, a 95% confidence interval will be calculated for the odds ratio. This confidence interval will be generated from a logistic regression model with ~~Clinical Success~~ as the primary variable, and treatment, stratum, and geographic region as the independent variables. If the lower limit of the 95% confidence interval for the odds ratio (BAY 41-6551/placebo) is greater than 1, BAY 41-6551 will be demonstrated to be statistically superior to placebo.

The individual components of the composite endpoint will be analyzed using Mantel-Haenzel ~~adjusting for stratum and geographic region. This is to assess if the components are moving in the same general direction and which, if any, single component is driving the result.~~

Tests will be performed using the SAS procedure FREQ, and the 95% confidence intervals for the odds ratios will be generated using PROC LOGISTIC.

An unadjusted chi-squared test will also be performed as a supportive efficacy analysis. In addition, a logistic regression model with only treatment as an independent variable will be performed, and the resulting 95% confidence interval for the odds ratio will be provided. These analyses will serve as sensitivity analyses to demonstrate consistency with the primary analysis.

The Breslow-Day test will be used as a further supportive analysis to test for treatment by geographic region and treatment by stratum interaction. If this test of the homogeneity of the odds ratio indicates a significant interaction, exploratory analyses will attempt to define its source. A Cochran-Mantel-Haenzel test of general association, adjusting for stratum and study protocol (ie, 13084 or 13085), will be performed to assess the effect of study protocol on the primary ~~outcome Clinical Success~~. Geographic region will not be included in this model as the 2 studies were conducted in different regions.

Exploratory descriptive summaries will be provided for the primary efficacy variable by treatment group and pre-determined subgroups of interest. These subgroups will include:

- Type of ventilator
- Underlying diagnosis
- Positive or negative blood culture
- CPIS (at pre-therapy)
- APACHE II score (< 20 , ≥ 20)
- Age (~~< 45 , $45-64$, ≥ 65~~)
- Sex
- Race
- Country
- ~~Body mass index (BMI) (< 25 , $25-30$, ≥ 30)~~
- ~~Baseline Gram-negative antibiotic treatment regimen (to be determined by actual baseline antibiotic usage; antibiotic groups will be determined before unblinding)~~

~~In addition, an analysis of Clinical Success will be conducted that excludes patients who received anti-microbial therapy considered to be effective against Gram-negative organisms, for infections other than the underlying pneumonia. Patients will only be excluded from this analysis if the additional anti-microbial therapy was administered before the TOC visit and the patient was not a Clinical Failure.~~

~~An additional descriptive exploratory analysis will be performed to compare the baseline characteristics of the patients who have the following TOC clinical responses:~~

- ~~Cure or failure~~
- ~~Indeterminate~~
- ~~Missing~~

~~Baseline characteristics will be shown by each of the three groups (cure/failure, indeterminate, missing). If the number of patients with indeterminate or missing responses is low, these groups will be combined.~~

New Text

The primary efficacy variable is Survival through the LFU visit. Survival is achieved when the patient is alive through the LFU visit. No other factors are considered in the evaluation of survival.

The primary analysis will compare the survival rates through LFU visit of patients in the BAY 41-6551 group versus patients in the placebo group, using the combined data from studies 13084 and 13085.

The null (H_0) and the alternative (H_1) hypothesis for this primary analysis is the following:

- $H_0: p[\text{BAY 41-6551}] = p[\text{placebo}]$
- $H_1: p[\text{BAY 41-6551}] \neq p[\text{placebo}]$

where p is the true Survival rate.

A Cochran-Mantel-Haenzel test of general association, adjusting for stratum and geographic region, will be performed as the primary efficacy analysis. If the p -value from this test is less than 0.05, and the proportion of patients who survive is higher in the BAY 41-6551 group than in the placebo group, the study will have achieved its primary objective.

In addition, as a supportive analysis, a 95% confidence interval will be calculated for the odds ratio. This confidence interval will be generated from a logistic regression model with Survival as the primary variable, and treatment, stratum, and geographic region as the independent variables. If the lower limit of the 95% confidence interval for the odds ratio (BAY 41-6551/placebo) is greater than 1, BAY 41-6551 will be demonstrated to be statistically superior to placebo.

Tests will be performed using the SAS procedure FREQ, and the 95% confidence intervals for the odds ratios will be generated using PROC LOGISTIC.

An unadjusted chi-squared test will also be performed as a supportive efficacy analysis. In addition, a logistic regression model with only treatment as an independent variable will be performed, and the resulting 95% confidence interval for the odds ratio will be provided. These analyses will serve as sensitivity analyses to demonstrate consistency with the primary analysis.

The Breslow-Day test will be used as a further supportive analysis to test for treatment by geographic region and treatment by stratum interaction. If this test of the homogeneity of the odds ratio indicates a significant interaction, exploratory analyses will attempt to define its source. A Cochran-Mantel-Haenzel test of general association, adjusting for stratum and study protocol (ie, 13084 or 13085), will be performed to assess the effect of study protocol on the primary efficacy variable Survival. Geographic region will not be included in this model as the 2 studies were conducted in different regions.

The primary efficacy analysis performed on the mITT population will be repeated for ITT population.

Exploratory descriptive summaries will be provided for the primary efficacy variable by treatment group and pre-determined subgroups of interest. These subgroups will include:

- Type of ventilator
- Underlying diagnosis
- Positive or negative blood culture
- CPIS at pre-therapy (< 6, 6, 7, 8, 9, 10, 11)
- APACHE II score (< 20, ≥ 20)
- Age (<18, 18 to <45, 45 to < 65, 65 to <75, ≥75 years)
- Sex
- Race
- Country
- Geographic region
- Latin America countries (Brazil, Colombia, Mexico)
- Asia Pacific countries (Philippines, South Korea, Taiwan, Thailand, China, Japan)
- Baseline Gram-negative antibiotic treatment taken by each patient (1, 2, >3)
- Primary reason for intubation (Current pneumonia-related respiratory failure vs everything else)
- Patients who received IV antibiotic for pneumonia ≥5 days after day of first intubation (Yes, No);
- Patients who received at least one dose of carbapenem during Days 1 through 10 (Yes, No);
- Start time of amikacin from start time of IV antibiotic (0 to <12 hours, 12 to <24 hours, >24 hours).
- Patients with confirmed MDR pathogens (MDR first detected at baseline, MDR first detected post-baseline, Not MDR);
- Patients with confirmed ESBL pathogens (ESBL first detected at baseline, ESBL first detected post-baseline, Not ESBL);

The last 2 subgroups above pertain to MDR designation which is described in detail in Appendix 9.1:

- To be declared a MDR, a bacterial isolate at the same visit must be resistant using the central laboratory interpretation to at least 3 of the 7 drug classes on the susceptibility panel: aminoglycoside, β-lactam/β-lactamase inhibitor, cepham,

carbapenam, tetracycline, folate pathway inhibitor, and quinolone. Once a patient has any MDR pathogen, he/she should be designated as a MDR patient no matter what the subsequent susceptibility tests show.

- For the 3 cephams (ceftazidime, cefazolin, and cefpodoxime), resistance to any one of the 3 drugs in the panel counts as cepham resistance for the category.
- An interpretation by central laboratory of “Not applicable” result will be considered as “susceptible” for purposes of MDR tabulation. This means that at least 3 results of “intermediate” or “resistant” are necessary for an MDR designation, and a “Not applicable” will not be included in the total.

Section 11.4 Methods for the Analysis of Secondary Efficacy Parameters – amended

Old Text

If the null hypothesis for the primary efficacy variable is rejected, a formal hypothesis testing scenario will be applied for the secondary efficacy variables:

- Pneumonia-related mortality through the LFU visit

...

For the purpose of the sequential testing procedure, the only effect in the models will be treatment. As supportive analyses, additional models will be used with effects included for geographic region for all secondary variables. Non-parametric tests for treatment comparisons will be considered as sensitivity analyses.

~~The other endpoints—total number of days of Gram-negative antibiotics, clinical response rates at end of therapy, change in component of CPIS score from baseline to TOC, microbiological eradication rates, the number of days in the hospital, and relapse rates will be summarized descriptively, however for the total number of days of Gram-negative antibiotics analysis of variance will be used to test the null hypothesis of no difference between BAY 41-6551 and placebo. In addition, Kaplan-Meier curves will be provided for time to Clinical Failure. The Investigator Assessment of Patient Outcome will be analyzed as sensitivity analysis.~~

New Text

If the null hypothesis for the primary efficacy variable is rejected, a formal hypothesis testing scenario will be applied for the secondary efficacy variables:

- Pneumonia-related mortality through the LFU visit (determined by blinded adjudication committee)

...

For the purpose of the sequential testing procedure, the only effect in the models will be treatment. As supportive analyses, additional models will be used with effects included for

geographic region for all secondary variables. Non-parametric tests for treatment comparisons will be considered as sensitivity analyses.

The secondary endpoint of pneumonia-related mortality through the LFU visit will be examined further by subgroups listed for the primary analysis.

All 4 secondary endpoints will be examined further by the following MDR subgroups:

- Patients with confirmed MDR pathogens (MDR first detected at baseline, MDR first detected post-baseline, Not MDR);
- Patients with confirmed ESBL pathogens (ESBL first detected at baseline, ESBL first detected post-baseline, Not ESBL);
- Patients who received IV antibiotic for pneumonia ≥ 5 days after day of first intubation (Yes, No);
- Patients who received at least one dose of carbapenem during Day 1 through 10 (Yes, No);
- Start time of amikacin from start time of IV antibiotic (0 to <12 hours, 12 to <24 hours, ≥ 24 hours).

The other efficacy endpoints are:

1. The number of days in the hospital through LFU visit
2. Relapse rates at LFU
3. Total number of days of Gram-negative antibiotics
4. Change in component of CPIS score from baseline to TOC
5. Clinical response rates at EOT (Clinical cure, Clinical failure)

Analysis of variance will be used to test the null hypothesis of no difference between BAY 41-6551 and placebo for the total number of days of Gram-negative antibiotics. The other four efficacy endpoints listed above will be summarized descriptively.

Section 11.5 Additional Analyses of Clinical Success - amended

Added Text

11.5 Additional Analyses of Clinical Success - amended

The following endpoints will be analyzed as additional analyses of clinical success:

11.5.1 Foundation for the National Institute of Health Criteria - amended

Clinical success using FNIH recommendations is defined as mITT patients who survived through the LFU visit and did not have septic shock. Patients will be designated as having a septic shock event based on the standard medical queries (SMQ) terms tabulated as adverse

events. Descriptive analysis will be provided with 95% confidence intervals. Cochran-Mantel-Haenszel test of general association adjusting for stratum and geographic region will also be performed.

11.5.2 Investigator Assessment of Patient Outcome - amended

Investigator Assessment of Patient Outcome is determined at the TOC visit. The outcomes of “success” or “failure” are based on the following criteria:

- Improvement or lack of progression of all abnormalities on chest radiograph
- Resolution towards normal of the following CPIS components: tracheal secretions (volume and purulence), temperature, blood leukocytes, oxygenation (P/F ratio)
- Any further change to the Gram-negative portion of the antimicrobial regimen being used to treat pneumonia during the first 10 days, after the initial antimicrobial adjustment within the first 96 hours after the initiation of empiric therapy or as soon as initial culture and susceptibility results are available and excepting the discontinuation of aminoglycosides after 5-7 days, would be considered a Clinical Failure
- Patient must not receive antibiotic therapy for pneumonia after Day 10 (EOT)
- Patient must survive through the TOC visit

All 5 conditions listed above must be met to achieve Investigator’s Assessment of Patient Outcome to be a Success. At the LFU visit, an assessment of relapse will be considered to be Failure.

These endpoints will be summarized descriptively with 95% confidence interval. A Cochran-Mantel-Haenszel test of general association adjusting for stratum and geographic region will be performed on the mITT patients.

In addition, Kaplan-Meier curves will be provided for time to Investigator Assessment of Clinical Failure. Time to Clinical Failure is defined as the time from the first day of study drug intake to the first time at which clinical failure is assessed. Patients who do not fail will be censored at death date, their LFU visit or last visit.

11.5.3 Clinical Success (Former 5 Component Primary Endpoint) - amended

Clinical Success is achieved when the following criteria are met as listed in the order of medical relevance:

- The patient must survive through the Late Follow-Up (LFU) visit
- Systemic antibiotics (IV or PO) for pneumonia must be stopped on or before the TOC visit (Day 17-19),
- Systemic antibiotics (IV or PO) for pneumonia must not be restarted after the TOC visit through the LFU visit
- The patient must have stable respiratory function evaluated at TOC or last visit based on the PaO₂/FiO₂ (P/F) ratio as outlined below (if P/F ratio is not available at the TOC, use the P/F ratio value from the closest previous visit), and

- The patient must not have a reported AE of lung abscess or empyema through the LFU visit

Stable respiratory function

- Patient is extubated at the TOC visit or
- Patient is intubated at the TOC and:
 - Patient has P/F ratio > 200 at the TOC visit or
 - Patient has P/F ratio > 100 and ≤ 200 at the TOC visit and:
 - Patient had a P/F ratio ≤ 200 at baseline

If ventilation status not explicitly known to be extubated for a patient at TOC or last visit, the status was assumed to be intubated for the determination of primary endpoint.

Unstable respiratory function

- Patient has a P/F ratio ≤ 100 at the TOC visit or
- Patient has a P/F ratio > 100 and ≤ 200 at the TOC visit and:
- Patient has P/F ratio > 200 at baseline

The outcome is Clinical Success if all 5 criteria are met. If any one of the criteria is not met, then the patient is considered a Clinical Failure. Patients who do not have a clinical assessment of success due to missing data will be considered a Clinical Failure.

For patients who discontinue study drug (on vent or handheld) for reasons other than efficacy will be handled as described in the table below:

<u>Reason for Discontinuation of Aerosol Therapy</u>	<u>Outcome / Comments</u>
<u>No Gram-negative bacteria isolated from a pre-therapy respiratory specimen</u>	<u>Patient is considered ITT analysis and not evaluated for efficacy analysis as mITT</u>
<u>Patient withdrew consent or refused handheld device</u>	<u>Evaluate for efficacy if all data for primary efficacy are available; if data are missing, then failure</u>
<u>Death</u>	<u>Failure</u>
<u>Adverse event</u>	<u>Failure</u>
<u>New therapy incompatible with aerosol therapy</u>	<u>Failure</u>
<u>Lost to follow-up</u>	<u>Failure</u>
<u>Any other reason/unknown reason</u>	<u>Failure</u>

Additional reasons for discontinuation may be included as failure after review of blinded data. The patient must have stable respiratory function evaluated at TOC or last visit based on the ventilation status and PaO₂/FiO₂ (P/F) ratio (if ventilation status or P/F ratio is not available at the TOC, use the respective ventilation status or P/F ratio value from the closest previous visit). See Section 6.2.1.1, Definition of Primary Efficacy Endpoint.

The analysis will compare the proportion of patients with Clinical Success in the BAY 41-6551 group versus the patients in the placebo group, using the combined data from studies 13084 and 13085. All assessments other than Clinical Success, which are, failures, improvements, and missing (those patients who do not have a TOC assessment) will be grouped together in the Clinical Failure category for the purpose of this analysis. If a TOC assessment is missing for determining the antibiotic criteria for a patient, the TOC assessment will be assumed to have occurred 17 days after the start of study drug.

A Cochran-Mantel-Haenszel test of general association, adjusting for stratum and geographic region, will be performed as the primary efficacy analysis. If the p-value from this test is less than 0.05, and the proportion of patients with Clinical Success is higher in the BAY 41-6551 group than in the placebo group, the study will have demonstrated superiority in this sensitivity analysis.

In addition, as a supportive analysis, a 95% confidence interval will be calculated for the odds ratio. This confidence interval will be generated from a logistic regression model with Clinical Success as the additional efficacy variable, and treatment, stratum, and geographic region as the independent variables. If the lower limit of the 95% confidence interval for the odds ratio (BAY 41-6551/placebo) is greater than 1, BAY 41-6551 will be demonstrated to be statistically superior to placebo.

Individual components of the composite endpoint will be analyzed using the Cochran-Mantel-Haenszel test adjusting for stratum and geographic region. This is to assess the components are moving in the same general direction and which, if any, single component is driving the result. The analysis of individual components will be performed on the actual counts of each criterion, not ordered by medical relevance.

Tests will be performed using the SAS procedure FREQ, and the 95% confidence intervals for the odds ratios will be generated using PROC LOGISTIC.

An unadjusted chi-squared test will also be performed as a supportive efficacy analysis. In addition, a logistic regression model with only treatment as an independent variable will be performed, and the resulting 95% confidence interval for the odds ratio will be provided.

The Breslow-Day test will be used as a further supportive analysis to test for treatment by geographic region and treatment by stratum interaction. If this test of the homogeneity of the odds ratio indicate significant interaction ($P < 0.10$), exploratory analyses will attempt to define its source.

A Cochran-Mantel-Haenszel test of general association, adjusting for stratum and study protocol (i.e., 13084 or 13085), will be performed to assess the effect of study protocol on the

