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

INHALE 1&2

BSP study drug:	BAY 41-6551 (Amikacin Solution for Inhalation and the Pulmonary Drug Delivery System [PDDS Clinical])
Study purpose:	Confirmatory for registration
Clinical study phase:	III Date: 3 November 2017
Study No.:	13084 & 13085 Version: 6
Author:	PPD

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Abbreviations

AE	Adverse events
AESI	Adverse event of special interest
APACHE II	Acute Physiology and Chronic Health Evaluation II
ATC	Anatomic Therapeutic Chemical Classification System
BAL	Bronchoalveolar lavage
BMI	Body Mass Index
CPIS	Clinical Pulmonary Infection Score
ECG	Electrocardiogram
eCRF	Electronic case report form
EOT	End of treatment
ESBL	Extended Spectrum Beta-Lactamase
FNIH	Foundation for the National Institute of Health
H0	Null hypothesis
H1	Alternative hypothesis
ICU	Intensive Care Unit
ITT	Intent to treat
IV	Intravenous
IVRS	Interactive Voice Response System
LFU	Late Follow-up
MDR	Multidrug resistant
MedDRA	Medical dictionary for regulatory activities
MIC	Minimum inhibitory concentration
mITT	Modified Intent to treat
MLG	MedDRA labeling groupings
N	Number
PDDS Clinical	Pulmonary Drug Delivery System
PaO_2/FiO_2 (P/F)	Ratio of arterial oxygen partial pressure to fractional inspired oxygen
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical Analysis plan
SAS	Statistical Analysis System
SD	Standard deviation
SI	International System of Units
SOC	System Organ Class
TA	Tracheal aspirate
TEAE	Treatment-emergent adverse event
TEAESI	Treatment-emergent adverse event of special interest
TOC	Test of cure
WBC	White blood cells
WHO-DD	World Health Organization-Drug Dictionary

1. Introduction

This statistical analysis plan describes the study objectives, study design, study population, efficacy and safety variables, statistical analysis methods, and study tables to be used in this study.

This version is based on study protocol 13084 amendment 8.0, version 9.0, dated 29 August 2017 and 13085 amendment 19, version 8.0, dated 29 August 2017 .

Inhaled amikacin as an adjunctive therapy to intravenously (IV) or intramuscularly (IM) (guideline directed) standard therapy for patients with gram-negative pneumonia may have potential to improve survival. Inhalation administration minimizes systemic exposure while delivering drug directly to the site of infection. This study will investigate the use of inhaled amikacin for the treatment of serious bacterial respiratory infections in intubated and mechanically-ventilated patients using a proprietary Pulmonary Drug Delivery System (PDDS Clinical).

2. Study Objectives

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 Survival as defined in protocol Section 8.2 and in Section 6.2.1.1 of this document. The secondary objectives are to evaluate the superiority of aerosolized BAY 41-6551 versus aerosolized placebo in clinical success rate, pneumonia-related mortality, the Early Clinical Response at Day 10, the days on ventilation, and the days in the ICU.

3. Study Design

3.1 Design Overview

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. All patients will receive standard of care IV antibiotic therapy with consideration to include 2 antibiotics as per the ATS/IDSA guidelines. 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.

A combined total of approximately 724 intent to treat (ITT) patients will be recruited to study 13084 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 in 1:1 ratio 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 modified intent to treat (mITT) patients in the primary efficacy analysis. The studies will be conducted at approximately 256 centers in North America, South America, Asia Pacific, Australia and Europe.

The duration of antibiotic therapy (both intravenous and aerosol) will be 10-12 full days; patients will be followed up to 28-32 Days after start of study drug. The end of the study for regulatory purposes is the date the last randomized patient completed the end of study visit.

Patients will be stratified by disease severity using the Acute Physiology and Chronic Health Evaluation (APACHE II) score (stratum I: APACHE II < 20, stratum II: APACHE II ≥ 20) by geographic region (or country). The APACHE II score that will be used to stratify the patient is the score calculated at the time the patient is evaluated for entry into the study. 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 period.

Once stratified, patients will be randomized in a double-blind fashion using a 1:1 allocation of patients to BAY 41-6551 versus placebo through the Interactive Voice Response System (IVRS).

No interim analysis is planned.

3.2　Schedule of Procedures – amended

Table 3–1 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 History	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 and 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[1]	X	X		X		X		X			X	X[s]	X[s]	X[r]	
Collection of ventilator parameters pre- and post-dose[2]		X	X	X	X	X	X	X	X	X[3]	X[4]				

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[1] Footnote s added with Protocol 13084 Amendment 6 and Protocol 13085 Amendment 16.

[2] Per Protocol 13084 Amendment 5 and Protocol 13085 Amendment 11

[3] Added with Protocol 13084 Amendment 6 and Protocol 13085 Amendment 16 as it was erroneously omitted.

[4] Added with Protocol 13084 Amendment 6 and Protocol 13085 Amendment 16 as it was erroneously omitted.

| 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
Collect respiratory specimen for Gram stain and culture[i]	X	X		X		X		X				X	X	X	X[r]	
Pleural fluid culture[j]	X															
CPIS[k]	X	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[5]											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; 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 posttherapy antibacterials, antifungals, and antivirals (within 2 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

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[5] Per Protocol 13084 Amendment 6 and Protocol 13085 Amendment 16

		Day										**Prematu re D/C/ Early Withdra wal**	**TOC Day 17 to 19**	**Late Follow-Up Day 28 to 32[b]**	
Assessment	**Screeni ng**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10[a] (EO T)**			**In Perso n**	**By Phon e**

[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 2 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 (e.g., 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.

[l] – *Footnote deleted per Amendment 16*

[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 one vial of study medication (either BAY 41-6551 or placebo) and one nebulizer/reservoir.[6]

[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 10 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.[7]

[p] - Serum amikacin for trough level will be obtained 30 ± 15 minutes[8] 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] - AE reporting begins after the signing of the informed consent by the patient or their legally authorized representative.

[r] - Optional assessments

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

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[6] Per Protocol 13084 Amendment 6 and Protocol 13085 Amendment 16

[7] Per Protocol 13084 Amendment 6 and Protocol 13085 Amendment 16

[8] "± 15" added with Protocol 13084 Amendment 6 and Protocol 13085 Amendment 16

In addition to the procedures listed above, pharmacokinetic sampling for BAY 41-6551 concentrations in tracheal aspirates, serum, and urine is performed in study #13085. The sampling scheme is outlined below.

Table 3–2 Sampling scheme of the PK substudy

Collection time on Day 1[a], 3 and 10[e] [hr]	Blood	Urine	Tracheal aspirate[b]
(30 minutes before first dose)	X	X[c]	X
0.25 ± 0.25 (after end of inhalation)	X		X
1.0 ± 0.5 (after end of inhalation)	X		X
2.0 ± 0.5 (after end of inhalation)	X		X
4.0 ± 1.5 (after end of inhalation	X		X (optional)
8.0 ± 2.0 (after end of inhalation)	X		
12.0 ± 2.0 (trough) (after end of inhalation)[d]	X		X

Abbreviations: hr = hour(s).

[a] blood sampling

[b] if feasible, (e.g. before patients are extubated)

[c] on Day 1 only: Urine samples should be taken from 0 to 12hr(s) and from 12 to 24hr(s)

[d] The blood sample for 12 hrs after the end of the inhalation must be collected before second dose

[e] Samples on Day 10 are optional but should be collected in case patients were switched to the hand-held inhalation device

Note: The first collection after end of inhalation is done after 30 minutes for China and EU and 15 minutes after for Japan.

3.3   Determination of Sample Size

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 (i.e., will not have a pre-therapy Gram-negative organism) a total of 362 ITT patients per group (724 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.

4. General Statistical Considerations

4.1   General Principles

The statistical evaluation will be performed by using the software package SAS release 9.1 or higher (SAS Institute Inc., Cary, NC, USA). Unless otherwise stated, all variables will be analyzed by descriptive statistical methods. The number of data available and missing data, mean, standard deviation, minimum, quartiles, median, and maximum will be calculated for continuous data. Frequency tables will be generated for categorical data.

All analyses are based on data from both studies 13084 and 13085 combined.

4.2   Handling of Dropouts

Premature discontinuations from study drug will be summarized by treatment group, both for any type of discontinuation, and for each specific reason for discontinuation. For the overall discontinuation rate, a chi-squared test will be used to test the null hypothesis of no differences in the discontinuation rates between treatment groups.

4.3   Handling of Missing Data

In order to achieve the goal of a well conducted clinical trial according to Good Clinical Practice (GCP), every effort should be made to collect all data. However, despite best efforts, it may be inevitable that missing or incomplete data are reported.

All missing or partial data will be presented in the patient data listings as they are recorded on the eCRF. Except as noted, missing data will not be imputed or carried forward in any statistical analysis. Missing responses for the secondary endpoints or additional analysis of clinical success will be included in the failure category. Missing responses can occur when the patients do not have a respiratory function assessment, and are not prematurely discontinued due to early treatment failure. Patients with missing data such that the primary endpoint assessment cannot be made are considered failures. This will also be the case for the secondary variable of early Clinical Response at the end of treatment (EOT) visit.

For the secondary and other efficacy endpoint variables related to duration of mechanical ventilation/intensive care unit (ICU)/in the hospital, the following approach will be used. If

the complete stop date of mechanical ventilation/ ICU/antibiotic therapy is not known, 28 days will be used for the calculation of the number of days.

For the Clinical Pulmonary Infection Score (CPIS) variable, a last observation carried forward (LOCF) approach will be used for patients with missing value at Days 3, 5, 10/EOT, TOC and LFU visits. The LOCF is being used as a conservative imputation, since the evaluations of CPIS early in the course of disease are generally worse than subsequent assessments later in the course of the disease. This LOCF method will be used for any missing individual components of the score. The CPIS will then be calculated using the available values, plus the carried-forward value(s) in place of the missing value(s).

For adverse events and concomitant medications, rules for handling missing or partial information will be implemented so as not to exclude patient data from analyses due to missing or missing or partially complete data. The general principle is as follows:

If an adverse event start date is completely missing or partially missing, then it assumed that the start date occurs at the earliest time on-treatment whenever possible.

If concomitant medication start date is completely missing, then the date is not imputed. Otherwise, if the concomitant medication start date is partially missing, then it is assumed that the start date occurs at the earliest time on-treatment whenever possible.

If a concomitant medication or adverse event stop date is completely missing or partially missing, then the stop date is imputed to maximize the duration of the event or concomitant treatment. It should be noted that imputation of stop dates only applies to concomitant medications that are not ongoing and adverse events that are not ongoing (i.e. outcome is not resolved).

4.4   Interim Analyses and Data Monitoring

No interim analyses for the purposes of evaluating efficacy are planned. A Data Monitoring Committee will be used to monitor safety findings. Only negative safety findings would result in stopping the trial early, and Bayer personnel will remain blinded.

4.5   Data Rules

Generally, for each date stored in database a set of organizational variables will be derived in order to describe the temporal context of that date in the specific study: Phase of treatment (pre, during or post study treatment), day relative to the start of study treatment, day relative to the end of study treatment.

Unless otherwise specified, baseline is defined as the last available value prior to the first dose of study treatment. Day 1 is assumed to be pre-dose if assessment time is not available. If assessment time is available, it will be used to determine pre-dose.

For the determination of visit of premature discontinuation, assignment of visits were based on the study day related to the corresponding scheduled visits.

Table 4–1 Assignment of visits

Study day	Visit (AVISIT)
< 1	Screening
1 to 9, inclusive	Day 1, 2, 3, 4, 5, 6, 7, 8, 9, respectively
10, 11	Day 10 / End of Treatment
17 to 19, inclusive	Test of Cure
28 to 32, inclusive	Late Follow-up

Refer to Section 4.3 for handling on missing data, as well as to Section 6.2, where for specific endpoints data rules are described, for example censoring subjects or definition of treatment-emergent AEs.

The countries will be pooled into the following geographical regions for purposes of subgroup and stratified analysis:

- North America – United States, Canada, and Australia

- Latin America – Brazil, Colombia, and Mexico

- Asia Pacific – Philippines, South Korea, Taiwan, Thailand, China, and Japan

- Europe – Czech Republic, Turkey, Belgium, Netherlands, France, Greece, Spain, Israel, Portugal, Hungary, Poland, Russia, and Ukraine.

The analysis described in this statistical analysis plan (SAP) will be performed for all geographical regions. A separate set of tables, figures and listings will be produced for each country requiring country analysis report (CAR).

4.6   Validity Review

The main concern of the validity review is to make sure that the mITT population, that is ITT population with a documented gram negative pathogen and have an APACHE II score $\geq$ 10, is well identified in the study. The results of the validity review meeting will be documented in the Validity Review Report and may comprise decisions and details relevant for statistical evaluation. Any changes to the statistical analysis prompted by the results of the validity review meeting will be documented in a supplement to this SAP, if applicable, or in the Clinical Study Report.

5. Analysis Sets

5.1   Assignment of analysis sets

The primary population for all efficacy analyses is the modified intent-to-treat (mITT) population, defined as all randomized patients with culture-confirmed Gram-negative bacteria who have been treated with at least one dose of study medication, and have an APACHE II score $\geq$ 10 at the time of diagnosis of pneumonia. Patients in the mITT population will be analyzed in the treatment group assigned. The ITT population is defined as all patients treated with at least one dose of study drug.

For efficacy analyses, patients in the ITT population will be analyzed in the treatment group assigned.

ITT for Safety population will be defined as ITT patients who will be analyzed as treated for safety analyses. Safety analysis will also be performed on mITT patients who will be analyzed as treated.

Pharmacokinetic dataset (PKS) includes ITT patients from whom a valid PK sample was obtained. This includes PK data from any of the 4 specimen types (tracheal aspirate, BAL, serum, urine) from both studies (13084 and 13085), i.e. also trough samples. Valid PK sample is determined by PK validity assessment.

These will be the only analysis populations in the study. No per protocol population is planned.

Invalid patients: only patients who do not receive any study medication will be considered invalid for this study.

Final decisions regarding the assignment of patients to analysis sets will be made during the Validity Review Meeting and documented in the Validity Review Report (see Section 4.6).

6. Statistical Methodology

6.1 Population characteristics

6.1.1 Disposition of patients

The number of patients enrolled will be tabulated by center and treatment group. Patient validity and primary reasons for exclusion from analysis will be summarized by treatment group.

A summary table will also be presented by the primary reason for discontinuation from screening for enrolled patients and at end of study for the randomized patients. Overview of patient disposition will be tabulated for all enrolled patients. As stated in Section 4.2, for the overall discontinuation rate, a chi-squared test will be used to test the null hypothesis of no differences in the discontinuation rates between treatment groups.

Protocol deviations by center will be tabulated.

6.1.2 Demographic and Baseline Characteristics

Demographic variables and baseline characteristics will be summarized descriptively for each treatment group separately and for all patients, in both the mITT and ITT populations. For continuous variables such as age, summary statistics will include N (number of patients contributing information), arithmetic mean, standard deviation (SD), median, minimum and maximum values. For categorical variables such as sex, frequency counts and percentages will be provided.

The following demographic data will be summarized:

- Age (year), Age category ((<18, 18 to <45, 45 to < 65, 65 to <75, ≥75)

- Sex

- Race and ethnicity

- Geographical regions (North America, Latin America, Asia Pacific, Europe)

- Latin America countries (Brazil, Colombia, Mexico)

- Asia Pacific countries (Philippines, South Korea, Taiwan, Thailand, China, Japan)

The following baseline characteristics will be summarized:

- Height (cm)

- Weight (kg)

- BMI (kg/m2), BMI group (<25, 25 to <30, ≥30)

- APACHE II score (< 20, ≥ 20)

- CPIS at pre-therapy (< 6, 6, 7, 8, 9, 10, 11)

- Type of tracheal device ((Endotracheal tube, Tracheostomy)

- Type of pneumonia (hospital acquired pneumonia; health-care associated pneumonia; ventilator associated pneumonia; community acquired pneumonia)

- Respiratory culture organisms also present in blood culture (Yes, No);

- Patients with confirmed multidrug resistant (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 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 to < 36 hours, 36 to ≥ 48 hours and missing).

The frequency of patients with baseline gram negative pathogens based on central laboratory results will be tabulated for ITT and mITT populations. Additionally, the proportion of ESBL pathogens from MIC testing will be tabulated.

6.1.3   Medical History

Medical histories will be tabulated by treatment group using Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 or higher version if available, summary statistics (frequency and percentage) will be provided by system organ class (SOC) and

preferred term (PT) for ITT and mITT populations. Clinical assessment of pneumonia at screening will be tabulated.

6.1.4   Concomitant Medications

Prior and concomitant medications will be coded using WHO-DD version 2005/Q3. Prior and concomitant medications will be tabulated by anatomical class and chemical level for the ITT and mITT populations. For the antibiotic medications, the coded medications will be reviewed by the project physician for appropriate mapping. Particular attention will be given to mapping of Gram negative antibiotics and to indication for current episode of pneumonia. Prior and concomitant antibiotics will be tabulated by indication and treatment group.

6.1.5   Study Medication Exposure

Study medication (total number of days; total number of doses; number of patients with one or more dose interruption and reasons) will be summarized descriptively by treatment group for ITT and mITT populations. Overall number of doses by administration device type will also be provided. Additionally, frequency of adjunctive therapy will be tabulated by treatment group. Duration will be calculated from the date of first study drug administration and continues through the last study drug administration. Medication interruptions will not be included. If a patient was extubated and re-intubated, the ventilator-free days will not be included in the calculation of the number of days on study drug via on-vent configuration.

6.2   Efficacy

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. Supportive efficacy analysis 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.

6.2.1   Primary Efficacy Endpoints

6.2.1.1   Definition of Primary Efficacy Endpoint

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.

6.2.1.2   Primary Efficacy Analysis

The primary analysis will compare the survival rates through LFU visit of patients in the BAY 41-6551 group versus the 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 [BAY 41-6551] = p[placebo]

H_1: p [BAY 41-6551] ≠ p[placebo]

where p is the true Survival rate.

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 who surviveis 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 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 primary outcome, 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.

6.2.1.3 Subgroup Analysis

Exploratory descriptive summaries will be provided for the primary efficacy variable (survive, death, and missing) by treatment group and pre-determined subgroups of interest, provided there is sufficient number of events in total within the subgroup across the treatment arms. These subgroups will include:

- type of ventilation (mechanical; mechanical and hand-held)

- underlying diagnosis (hospital acquired pneumonia; health-care associated pneumonia; ventilator associated pneumonia; community acquired pneumonia)

- Blood culture (positive = presence of GN pathogen at screening or baseline; negative = absence of GN pathogen at screening or baseline)

- CPIS at pre-therapy (< 6, 6, 7, 8, 9, 10, 11)

- APACHE II score at pre-therapy (< 20; ≥ 20)

- Age (< 18, 18 to < 45, 45 to < 65, 65 to < 75, ≥ 75 years)

- Sex

- Race

- Body mass index (BMI) (< 25; 25-< 30; ≥ 30 kg/m2)

- 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 A:

- 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 6 drug classes on the susceptibility panel: aminoglycoside, β-lactam/β-lactamase inhibitor, cephams, 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.

6.2.2   Secondary Efficacy Endpoints

The following secondary endpoints will be tested sequentially in the order listed if the null hypothesis for the primary endpoint is rejected.

- Adjudicated pneumonia-related mortality through LFU visit as determined by blinded adjudication committee

- Early Clinical Response (based on CPIS, mortality, and presence of empyema or pulmonary abscess through the EOT visit)

- The number of days on mechanical ventilation through the LFU visit

- The number of days in the ICU through the LFU visit

Early Clinical Response will be determined by the following:

1) CPIS scoring at days 3, 5, and 10 compared to baseline as follows:

- On Day 3, CPIS increase from baseline by at least 2 points is considered a failure

- On Day 5, CPIS decrease from baseline of at least 1 point is not a failure. CPIS of no change from baseline is considered a failure. Any CPIS increase from baseline is a failure.

- On Day 10, CPIS decrease from baseline of at least 2 points is not a failure. CPIS decrease of only 1 point is a failure. CPIS of no change is considered a failure. Any CPIS increase from baseline is a failure.

A failure at any one of the three CPIS evaluations on days 3, 5 or 10 makes the patient a failure for the early clinical response.

2) All-cause mortality through the EOT visit is a failure.

3) The development of empyema or lung abscess through the EOT visit is a failure.

The Early Clinical Response is a success if all three of the CPIS determinations are not failures, and the all-cause mortality and empyema and lung abscess variables are absent. If any one of the Early Clinical Response evaluations is a failure, then the patient is a failure for Early Clinical Response.

The number of days on mechanical ventilation and the number of days in ICU are calculated from the date of first study drug administration and continue through the LFU visit. If a patient was extubated and re-intubated during the 28 day study period, the ventilator free days will not be included. If the complete date of stop date of mechanical ventilation/ICU is not known for a patient, the 28 days will be used for the number of days. For patients who died,

the number of days on ventilation will be censored at 28 days. For patients who lived through LFU visit, the ventilation days are 28 days.

6.2.2.1 Secondary Efficacy Analysis

The secondary efficacy endpoint 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 in the mITT and ITT populations, except as noted below. A sequential testing procedure will be performed at the two-sided alpha level of 0.05 for the four secondary efficacy variables, strictly in the order listed above.

The null hypothesis of no difference between BAY 41-6551 and placebo in adjudicated pneumonia-related mortality and early clinical response will be tested using an unadjusted Chi-square test in the mITT population.

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 the number of days in the ICU.

For the purpose of the sequential 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 comparison 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 in Section 6.2.1.3. 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 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).

Number of days on mechanical ventilator will be summarized by descriptive statistics. Duration will be defined as the number of days from the date of first study drug through the LFU visit. For patients who lived through the LFU visit, the ventilation days are actual days on ventilation with a maximum value of 28 days. For patients who died after Day 28, but on or before their LFU visit, the days on ventilator is censored at 28 days. For patients who died or discontinued off-ventilation, the number of days on ventilation is actual days on ventilation

with a maximum value of 28 days. For patients who died or discontinued on-ventilation, the number of days on ventilation will be 28 days. Further analysis of the number of days on mechanical ventilator will be performed with censoring at Day 28 for subset of patients on ventilation without censoring.

Patient status at the LFU visit will also be summarized, where the status will be dead, ventilated and in ICU, off-ventilation in ICU, and off ventilation in hospital (not ICU).

Number of days on ICU will be summarized by descriptive statistics. Duration will be defined as the number of days from the date of first study drug through the LFU visit. For patients who lived in ICU through the LFU visit, the ICU days are actual days in ICU with a maximum value of 28 days. For patients who died after Day 28, but on or before their LFU visit, the days in ICU is censored at 28 days. For patients who died or discontinued in ICU, the number of days in ICU will be 28 days. Further analysis of the number of days in ICU will be performed with censoring at Day 28 for subset of patients on ventilation and without censoring.

6.2.3   Other Efficacy Analysis

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. All cause mortality rates at EOT

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. Other secondary endpoints will be summarized descriptively.

6.2.4   Additional Analysis of Clinical Success

6.2.4.1 Foundation for the National Institute of Health (FNIH) Criteria

Clinical success using FNIH recommendation will be 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.

6.2.4.2 Investigator Assessment of Patient Outcome

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 to7 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.

This endpoint 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.

6.2.4.3 Clinical Response Endpoint - 5 component endpoint

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 PaO_2/FiO_2 (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:

    o Patient has P/F ratio > 200 at the TOC visit or

    o Patient has P/F ratio > 100 and ≤ 200 at the TOC visit and

    o 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:

    o 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:

Table 6–1 Outcome of patients who discontinue study drug

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 PaO_2/FiO_2 (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).

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, that is, failures, improvements, and missings (those patients who do not have a TOC assessment) will be grouped together in the Clincial 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 additional analysis of success. 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 Sucess as the additional analysis of success 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 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.

6.2.5 Microbiological Analysis

Organism identifications generated by the central laboratory will be used as the primary source for microbiological endpoints. Local laboratory results will not be used for analysis.

Microbiology related endpoints:

There are 7 microbiology related endpoints. All of these are secondary endpoints.

Secondary microbiological objectives will include comparisons (aerosolized BAY 41-6551 versus aerosolized placebo), as adjunctive therapy in the mITT population in the following analysis:

1. Microbiological response by pathogen at the TOC and LFU visit
2. Microbiological response by patient at the TOC and LFU visit
3. Clinical response by pathogen and patient at the LFU visit
4. Emergence of new respiratory pathogens during the aerosol treatment period, Days 1-10
5. Amikacin resistance among pathogens by patient (baseline, EOT, TOC, LFU)
6. Clinical Response by MIC value of amikacin by patient and pathogen
7. Clinical response in Monomicrobic versus polymicrobic infections

By-patient and by-pathogen bacteriological eradication rates at the TOC visit will be provided by treatment group in the mITT population.

Microbiological responses are based on culture results from the central laboratory and utilize the following terms:

- **Eradication**: the absence of the original pathogen(s) at the post-treatment TOC or LFU culture of specimens from the original site of infection (tracheal aspirate/sputum)

- **Presumed eradication**: no culture results available/culture not taken in a patient judged to be a Clinical Success (survival); [patient is unable to produce sputum and invasive procedures are not warranted]

- **Persistence**: the presence of the original pathogen from the post-treatment TOC or LFU culture specimens from the original site of infection

- **Presumed persistence**: no culture results available/culture not taken in a patient judged to be a Clinical Failure (mortality) and invasive procedures are not warranted

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

6.2.5.1   Microbiological response by baseline pathogen from respiratory sample at the TOC and LFU visit.

For microbiological responses by pathogen, the percentage of patients with microbiological response for each pathogen among the total number of patients with baseline pathogen isolates for each pathogen will be determined. If a patient has 3 pathogens, all 3 are tabulated.

Bacteriological eradication rate is defined as (eradication and presumed eradication)

divided by the sum of (eradication + presumed eradication + persistence + presumed persistence + indeterminate (all total outcomes)). Similarly, other microbiological response rates will be calculated.

The data is displayed for each bacterial genus/species.

Baseline pathogen is defined as pathogens tested at screening and Day 1 visit by central laboratory.

6.2.5.2   Microbiological response by patient at the TOC and LFU visit.

For microbiological responses by patient, the percentage of patients with microbiological response among mITT patients will be determined

- The responses of eradication, presumed eradication are tabulated for each patient.
- All pathogen isolates from an individual patient must be eradicated (or presumed eradicated) to tabulate an eradicated (or presumed eradicated) response.

If one or more pathogen persists (or presumed persists), all isolates from a patient are tabulated as "persistence" (or presumed persistence). Bacteriological eradication rate is defined as (eradication and presumed eradication) divided by the sum of (eradication + presumed eradication + persistence + presumed persistence + indeterminate (i.e. all total outcomes)). Similarly, other microbiological response rates will be calculated.

The data is displayed for each individual bacterial genus/species.

6.2.5.3   Clinical response by pathogen and patient at the LFU visit.

In addition to the microbiological response by pathogen, the clinical response by pathogen and patient is displayed. This evaluation uses the same clinical response criteria (survival) as the primary end point on the mITT population subdivided by pathogen. This evaluation can only be done on the LFU visit, since that is when the primary clinical response is evaluated. The percentage of patients with indicated baseline isolate tabulated as Clinical Success among the total number of patients with the indicated baseline pathogen isolates will be determined.

6.2.5.4   Emergence of new respiratory pathogens after start of study drug

Rates of emergent of new bacterial species (superinfection) after start of study drug will be summarized by treatment group. This will include a summary of new bacterial genus/species

which occur after start of study drug. By patient and by-organism displays will be provided for each treatment group for each type of emergent infection.

6.2.5.5   Amikacin resistance among pathogens by patient (baseline, EOT, TOC, LFU).

Resistance to Amikacin is determined for the bacterial isolates by using a standardized microbiology laboratory test that generates a minimum inhibitory concentration (MIC) for amikacin and bacterial isolate. For the INHALE trials, the MIC values of amikacin are important in tracking resistance. Fortunately, the same microbiology resistance standard is used for all bacteria tested against amikacin.

Resistant bacteria have a MIC value of 64 µg/mL or greater. Percentages of resistance are calculated based on the percentage of patients infected with pathogens resistant to amikacin at the different trial points (baseline, EOT, TOC, LFU). Resistance as determined by central laboratory is displayed for each bacterial genus/species. Rates of baseline pathogens at the baseline MIC with microbiological assessment at TOC visit of eradicated or presumed eradicated (or persistent or presumed persistent) among the total number of pathogens for the MIC at baseline will be determined for the amikacin group.

6.2.5.6   Clinical Response by MIC value by patient and pathogen

Results of pre-therapy Amikacin sensitivity testing by baseline genus/species and primary clinical response (survival/mortality at LFU) will be presented for each baseline pathogen from respiratory sample collection displayed by MIC at baseline for Clinical Success and failures. For each pathogen, the percentage of baseline pathogen at the MIC with Clinical Success or Clinical Failure among the total number of pathogen for the MIC will be displayed.

6.2.5.7   Clinical response for monomicrobic versus polymicrobic infections at LFU.

- Patients with 1 pathogen at baseline considered monomicrobic
- Patients with >1 baseline pathogen considered polymicrobic

The Clinical Success response for monomicrobial and polymicrobial infections is displayed. This evaluation uses the same clinical response criteria as the primary end point on the mITT population subdivided by monomicrobial and polymicrobial infections. This evaluation can only be done on the LFU visit, since that is when the primary clinical response is evaluated. The clinical response is displayed for each bacterial genus/species.

6.2.5.8   Additional microbiological analysis

Additional analyses include the following:

- Summary of clinical response for Gram negative and mixed infections,

- Summary of treatment-emergent resistance to amikacin displays the number of patients who had specific pathogen that was susceptible to amikacin in pre-treatment period and resistant or indeterminate to amikacin in treatment or post-treatment period or patients who had indeterminate in pre-treatment period and resistant in treatment or post-treatment period.

- Summary of new pulmonary pathogens include the number of patients with new pathogen (not the original pathogen) from a specimen after the patient has completed antibiotic therapy.

6.3 Mortality

Mortality rates will be summarized through the LFU visit, through the TOC visit, during therapy, through day 15 and through day 28 by treatment group for the ITT and mITT populations. 95% confidence intervals will also be provided for the difference between groups in mortality rates at these time points. Normal approximations to the binomial distribution will be used to generate the confidence intervals.

Time to death will be provided for observed time for patients who died. Kaplan-Meier curves will be provided for time to death for all patients. Time to death is defined as the time from the first day of study drug intake to death. Patients alive during the study are censored at LFU visit or last visit date Causes of death will be summarized through the LFU visit, through the TOC visit, during therapy, through day 15 and through day 28. If a patient did not have TOC visit, day 17 will be used as a cut-point for determining mortality at TOC visit. If a patient did not have EOT visit, day 10 will be used as a cut-point for determining mortality at EOT.

6.4 Pharmacokinetics / pharmacodynamics

PK summary statistics

Summary statistics of valid concentrations of amikacin from serum, tracheal aspirate, and urine samples in the PKS population will be provided for each assessment time point. All patients had PK assessment at trough (pre-dose) only, whereas patients in the PK substudy had PK assessments at all time points. Separate summaries will be provided for patients who received amikacin by inhalation only, patients who received amikacin by inhalation with amikacin IV as concomitant medication, and as those who received amikacin IV as concomitant medication only. Plot of geometric mean and geometric SD of trough serum concentration of amikacin over the entire study duration will be provided. Means at any time will only be calculated if at least 2/3 of the individual data were measured and were above the lower limit of quantification (LLOQ). For the calculation of the mean value a data point below LLOQ will be substituted by one half of this limit. In tables showing mean values, where values below LLOQ are included in the calculation of mean values, these means willbe flagged.

PK analysis for blood, serum and urine samples

Exploratory population PK and pharmacokinetic/pharmacodynamic (PK/PD) modeling will be performed to describe amikacin pharmacokinetics using population approaches (e.g.

NONMEM). This analysis will include an investigation of potential inter-ethnic differences in the pharmacokinetics of amikacin. The influence of relevant patient covariables such as age, gender, or body weight, or potentially relating parameters of clinical efficacy response to amikacin serum concentrations will also be evaluated.

Population PK for TA and respiratory secretions

PK/PD modeling using population approach, e.g. NONMEM, will be performed to describe PK/PD including potential influence of relevant patient co-variables (e.g. inter-ethnic differences, age, gender, etc.)

The corresponding investigations for serum, urine, bronchoalveolar lavage (BAL), and tracheal aspirate (TA) will be described and reported under separate cover.

6.5   Safety

All analyses of safety endpoints will be descriptive only; no formal testing will be performed. All safety tabulations will be produced for the ITT for Safety population grouped as treated, as well as for the mITT population as treated.

6.5.1   Adverse Events

An assessment of the safety of treatment will be conducted based on the comparison of treatment groups for the ITT for Safety population grouped as treated, and the mITT population grouped as treated with respect to the incidence of all treatment-emergent adverse events and, separately, all drug-related and device-related treatment-emergent adverse events. All AEs will be coded using the MedDRA dictionary Version 18 or higher.

AE and serious AE (SAE) will be considered treatment-emergent if they occur any time after the first dose of therapy, through 7 days after the end of treatment. The incidence of AEs will be described by SOC and preferred term (PT) within the SOC. Additionally, SAEs up to LFU (Day 28 visit) will be presented by SOC and PT.

A table will summarize the overall number and percentage of patients with at least 1 of the following AEs, where patients with more than 1 AE in a particular category are counted only once in that category for the ITT for Safety population grouped as treated and the mITT population grouped as treated:

- Any AE

- Any study drug-related AE

- Any SAE

- Any study drug-related SAE

For each of the above AE category -

- AE by intensity

- AE by worst outcome

- Any AEs leading to study drug discontinuation

- Any SAEs leading to study drug discontinuation

- Any device-related AE

- Any device-related SAE

- Any device related serious AE

- Any study procedure-related AE

- Any study procedure-related SAE

Similar overall table will be summarized for TEAE for the ITT for Safety population grouped as treated, and the mITT population grouped as treated.

For the summary by intensity, patient with multiple occurrences of the same event will be counted once at their maximum intensity within a SOC and PT.

The number and percentage of patients reporting each AE and TEAE will be summarized by SOC and PT for the ITT for Safety population and the mITT population as specifed. Tables will be sorted alphabetically by SOC. PTs will be sorted by descending overall total. The following summaries will be produced:

- AE by SOC and PT for ITT and mITT

- SAE by SOC and PT for ITT and mITT

- AE leading to drug withdrawal by SOC and PT for ITT and mITT

- AE resulting in death by SOC and PT for ITT and mITT

- AE by maximum intensity, SOC and PT for ITT and mITT

- Serious AE by maximum intensity, SOC and PT for ITT and mITT

- AE by worst outcome, SOC and PT for ITT and mITT

- Serious AE by worst outcome, SOC and PT for ITT and mITT

- TEAE by SOC and PT for ITT and mITT

- Drug-related TEAE by SOC and PT for ITT

- Device-related TEAE by SOC and PT for ITT

- Study procedure-related TEAE by SOC and PT for ITT

- Serious TEAE by SOC and PT for ITT and mITT

- Drug-related serious TEAE by SOC and PT for ITT

- Device-related serious TEAE by SOC and PT for ITT

- Study procedure-related serious TEAE by SOC and PT

- TEAE leading to drug withdrawal by SOC and PT for ITT and mITT

- TEAE resulting in death by SOC and PT for ITT and mITT

- TEAE by maximum intensity, SOC and PT for ITT and mITT

- Serious TEAE by maximum intensity, SOC and PT for ITT and mITT

- Drug-related TEAE by maximum intensity, SOC and PT for ITT

- TEAE by worst outcome, SOC and PT for ITT and mITT

- Serious TEAE by worst outcome, SOC and PT for ITT and mITT

Tables will be produced displaying the incidences of AE or TEAE, drug-related TEAE, device-related TEAE and study procedure-related TEAE by MedDRA labeling groupings (MLG), i.e. sponsor defined groupings of MedDRA preferred terms by primary SOC. A separate overview table will be created showing the PTs belonging to all MLGs.

The overall proportion of patients with any TEAE identified as organ failure will be summarized, as well as the proportion of patients in each specific type of organ failure by SOC and PT for ITT and mITT for safety population. Similar display will be summarized for AE identified as organ failure. Organ failure is defined by organ type, by a collection of MedDRA preferred terms determined by the Bayer clinical team and listed in Appendix B of this document.

The overall proportion of patients with bronchial hyperreactivity will be compared with patients without bronchial hyperreactivity. Bronchial hyperreactivity was defined by the clinical team and listed in Appendix C of this document. Overall summary tables as well as summaries by SOC and PT for TEAE, serious TEAE, study drug-related TEAE, and drug-related serious TEAE will be provided.

Adverse events of special safety interest (AESI) are those identified as risks of parenteral (IV and IM) formulations of the study treatment (e.g., neurotoxicity, ototoxicity, and nephrotoxicity). AEs due to local exposure in the bronchopulmonary system, such as bronchospasm, coughing during or shortly after inhalation of aerosol, and hemoptysis are also considered AESI. An overview table will be provided listing PTs belonging to sponsor defined MedDRA term groupings for each topic of special interest for ITT and mITT for safety group. TEAE of special interest (TEAESI) will be summarized by safety topic and PT:

- TEAESI by safety topic and PT

- TEAESI by maximum intensity

- TEAESI by worst outcome.

Table 6–2 Safety topics of special interest

Topic	Adverse events of special safety interest
Localized adverse effects to the respiratory tract (excluding bronchospasm)	PBMQ 'Localized adverse effects to the respiratory tract (Amikacin Inhale)' (SMQ code=SMQ_1610) excluding 'Bronchospasm (Amikacin Inhale)' (SMQ code = SMQ_1608) but including MLG 'Respiratory tract hemorrhage' (SMQ code=SMQ_0163)
Bronchospasm	PBMQ 'Bronchospasm (Amikacin Inhale)' (SMQ code = SMQ_1608)
Device-related events	All AEs that were reported as device-related by the investigator
Nephrotoxicity	SMQ 'Acute renal failure (SMQ)' (SMQ code=20000003)
Hypersensitivity/Anaphylactic reactions	PBMQ 'Hypersensitivity type I and IV and anaphylactic reactions (Amikacin Inhale)' (SMQ code = SMQ_1607)
Ototoxicity/Vestibular toxicity	SMQ 'Hearing impairment (SMQ)' (SMQ code=20000171) SMQ 'Vestibular disorders (SMQ)' (SMQ code=20000172)
Neuromuscular Blockade / Neurotoxicity	PBMQ 'Peripheral neurotoxicity and neuromuscular blockade (Amikacin/Aminoglycosides)' (SMQ code = SMQ_1612)

Patient listings of all AE as well as subset listings of device-related AEs, treatment-related AEs, SAEs with outcome of death, SAEs, device-related AEs, SAEs resulting in study drug discontinuation, procedure-related SAEs, and drug related SAEs will be provided.

6.5.2   Device Events

Device evaluation results as reported in the eCRF will be summarized by device event category and treatment group. The incident evaluation (incident, near incident, non-incident, missing, and associated with AE/SAE) of device events among the ITT for safety population will be presented by the number of study drug dose and treatment group. Percentage of event category (device malfunction, use error or handling difficulty, and other device event) for each incident evaluations will be presented. Additionally, the number of patients with at least one event will be summarized in each category.

6.5.3   Laboratory Data

Laboratory data will be analyzed descriptively for the ITT population and mITT population grouped as treated using International System of Units (SI). The absolute values and changes from baseline will be summarized for each treatment group using N (number of patients contributing information), arithmetic mean, standard deviation (SD), median, minimum and maximum values for each visit. If multiple assessments are made during a treatment visit, the last scheduled or unscheduled assessment will be included in the summary. For analysis purposes, values preceded by a ">"sign (i.e. those above the limits of quantification) will be considered equal to the upper limit of quantification. Values preceded by a "<" sign (below the limits of quantification) will be substituted with ½ the limit of quantification for the calculation of descriptive statistics. Urinalysis tests will be summarized by frequency of categorical results at each visit.

Creatinine clearance is calculated using Modifications of Diet in Renal Disease (MDRD) method, where GFR = 175 x serum creatinine ** -1.154 x age ** (-0.203) x (1.212 if Black) x (0.742 if female).

Number of patients with acute kidney injury (AKI) will be summarized for patients with baseline APACHE II score of No for acute renal failure. For patients with normal serum creatinine at baseline, AKI is defined as an increase of 0.3 mg/dL in creatinine from baseline. For patients with abnormal baseline serum creatinine, AKI is defined as an increase of 50% from baseline.

Additionally, a summary of number of patients with treatment emergent abnormally low values and treatment emergent abnormally high values will be provided by laboratory test.

Pregnancy information was summarized by treatment group.

6.5.4   Vital Signs

Vital sign data will be analyzed descriptively for the ITT population and the mITT population grouped as treated. The absolute values and changes from baseline will be summarized for each treatment group using N (number of patients contributing information), arithmetic mean, standard deviation (SD), median, minimum and maximum values for each visit. Baseline values will be defined as the last pre-dose assessment. Mean of the assessment will not be used. If multiple assessments are made during a treatment visit, the last scheduled or unscheduled assessment will be included in the summary.

6.5.5   ECG Data

ECG data will not be collected in this study.

6.6   Additional analyses

Not Applicable.

7.   Document history and changes in the planned statistical analysis

Table 7–1 Document history and changes in the planned statistical analysis

Document Version / Date	Changes	Reason of Changes
Version 1.0 / 16 March 2011	Combined SAP for both studies 13084 and 13085	Not applicable
Version 2.0 / 10 Feb 2015 for 13084 only	Sample size change from 650 to 662; patients in mITT populations changed from 520 to 430.	Changes based on the protocol amendment dated 17 September 2014
Version 2.0 / 10 Feb 2015 for 13084 only	Geographic region (or country) added as a randomization stratification factor.	Changes based on the protocol amendment dated 17 September 2014
Version 2.0 / 10 Feb 2015 for 13084 only	Regional definitions modified to reflect different countries included in the study.	Changes based on the protocol amendment dated 17 September 2014
Version 2.0 / 10 Feb 2015 for 13084 and 13085	Odds ratio analysis clarified to be a supportive analysis only.	Changes based on the protocol amendment dated 17 September 2014
Version 2.0 / 10 Feb 2015 for	Variables in the formal	Changes based on the protocol

Document Version / Date	Changes	Reason of Changes
13084 only	secondary analysis hypothesis testing algorithm modified – relapse rates and hospital days added, number of antibiotic days and change in CPIS removed.	amendment dated 17 September 2014
Version 2.0 / 10 Feb 2015 for 13084 only	Treatment emergent AE definition clarified.	Changes based on the protocol amendment dated 17 September 2014
Version 4 / 19 Feb 2016	Study Objectives revised to match wording in the protocol.	Changes based on the protocol amendment 6, Version 7.0 8 February 2016.
Version 4 / 19 Feb 2016	Study Design Overview revised reflects combined study 13084 and 13085. Sample size change from 662 to 724 ITT; patients in mITT populations changed from 430 to 472.	Changes based on the protocol amendment 6, Version 7.0 8 February 2016.
Version 4 / 19 Feb 2016	Schedule of Procedures added.	Changes based on the protocol amendment 6, Version 7.0 8 February 2016.
Version 4 / 19 Feb 2016	Sample size recalculated for combined study.	Changes based on the protocol amendment 6, Version 7.0 8 February 2016.
Version 4 / 19 Feb 2016	Handling of Dropouts	Added details.
Version 4 / 19 Feb 2016	Handling of Missing Data	Added details
Version 4 / 19 Feb 2016	Data Rules geographical regions were revised	Changes based on the protocol amendment 6, Version 7.0 8 February 2016.
Version 4 / 19 Feb 2016	Disposition of Patients section added.	Added details.
Version 4 / 19 Feb 2016	Sections on Demographic and Baseline Characteristics; Medical History, Concomitant Medication, Study Medication Exposure, Adverse Events, Laboratory Data, Vital Signs	Added details.
Version 4 / 2 Mar 2016	Efficacy sections	Changes based on study protocol 13084 amendment 6.0, version 7.0, dated 29 February 2016 and 13085 amendment 16, version 6.0, dated 29 February 2016.
Version 5 / 19 May 2016	Efficacy sections	Changes based on study protocol 13084 amendment 7.0, version 7.0, dated 16 May 2016 and 13085 amendment 16, version 6.0, dated 16 May 2016
Version 6 / 3 April 2017	Study Design.	Clarified stratification as country rather than region.
Version 6 / 3 April 2017	Data Rules	Clarified baseline definition and deleted a sentence on country-

Document Version / Date	Changes	Reason of Changes
		specific analysis.
Version 6 / 3 April 2017	Demographic and Baseline Characteristics	Revised subgroups for respiratory culture organisms and added 5 subgroups pertaining to MDR.
Version 6 / 3 April 2017	Concomitant medications	Clarified coding of concomitant medications and antibiotics.
Version 6 / 3 April 2017	Study Medication Exposure	Added details of analysis.
Version 6 / 3 April 2017	Efficacy	Ordered primary efficacy criteria by medical relevance. Added ventilation status assumption. Added handling of missing TOC visit for endpoint criteria regarding systemic antibiotics. Added details on additional efficacy analyses. Added subgroups for MDR and details of derivation of MDR patients for primary and secondary analyses. Added details on secondary efficacy analyses. Added exploratory analysis of primary efficacy endpoint.
Version 6 / 3 April 2017	Microbiological Analysis	Clarified analysis and added descriptions of additional analyses
Version 6 / 3 April 2017	Mortality	Added details of analysis
Version 6 / 21 April 2017	Adverse events	Added condition for TEAE. Added details of analyses. Added summary by MLG. Added analysis by bronchial hyperreactivity. Added table defining AE of special interest.
Version 6 / 21 April 2017	Laboratory Data	Added urinalysis summary. Added definition of creatinine clearance. Added AKI.
Version 6 / 21 April 2017	Appendices	Added list of terms for organ failure. Added list of terms for bronchial hyperreactivity
Version 6 / 21 April 2017	Device events	Added details for device event analysis: summary by event/no. of doses; summary by event / no. of patients; summary by category; summary by event; summary by event related to AE/SAE
Version 6 / 28 June 2017	Header	Revised study number and

Document Version / Date	Changes	Reason of Changes
		header format to be consistent with CSR header.
Version 6 / 28 July 2017	Efficacy	Changes based on the protocol amendment 6, Version 7.0 8 February 2016.
		New primary endpoint added
		Moved previous primary endpoint to Additional Efficacy Endpoint Analysis
Version 6 / 2 Aug 2017	6.5.4 Vital Signs	Clarified definition of baseline
Version 6 / 2 Aug 2017	4.5 Data Rules	Clarified the assignment of visit for discontinuation
		Clarified the definition of baseline
Version 6 / 16 Oct 2017		Amended according to the new primray endpoint described in protocol amendment.
Version 6 / 20 Oct 2017		Added AE and TEAE summaries for mITT population grouped as treated.
Version 6 / 3 Nov 2017	Introduction	Fixed 13084 amendment and version numbers.
Version 6 / 3 Nov 2017	6.5.1 Adverse events	Deleted duplicate bullet lines. Added mITT to organ failure and AE of special interest

8.   References

None.

9.   Appendices

9.1 Appendix A: MDR Subgroup Analysis Plan

Table 9–1 MDR Subgroup Analysis Plan

Subgroups	Groups defined as	Analysis to be provided
Patients with confirmed MDR pathogens	See next page for definitions. • MDR first detected at baseline • MDR first detected post baseline • Not MDR	a) Descriptive statistics b) Survival c) Pneumonia-related mortality d) Early clinical response e) Vent days f) ICU days
Patients with confirmed ESBL pathogens (identified by Covance microbiology lab)	See next page for definitions. • ESBL first detected at baseline • ESBL first detected post baseline • Not ESBL	a) Descriptive statistics b) Survival c) Pneumonia-related mortality d) Early clinical response e) Vent days f) ICU days
Late onset of infection on the vent: >d5 If a patient was intubated on multiple dates, use the earliest occurrence of start of intubation. If intubation date or antibiotic start date is completely missing, the date will not be imputed and the response will be No. If partial intubation date, impute to earlier of first study drug date, 1st of month (if dd is missing), 1JAN (if dd and mmm is missing). If patient received antibiotic on multiple dates, use the earliest occurrence after intubation.	Patients who received IV antibiotic for pneumonia 5 or more days after day of intubation. • Yes • No (includes those with < 5 days and no IV antibiotics for pneumonia)	a) Descriptive statistics b) Survival c) Pneumonia-related mortality d) Early clinical response e) Vent days f) ICU days

Subgroups	Groups defined as	Analysis to be provided
Cochrane review on VAP 2016 showed only carbapenem-use shows a difference in clinical cure: All patients that were NOT treated with with IV-carbapenems CMATC01 (ATC Code 01) = CARBAPENEMS	Patients who received at least one dose of carbapenem during Days 1 through 10 • Yes • No	a) Descriptive statistics b) Survival c) Pneumonia-related mortality d) Early clinical response e) Vent days f) ICU days
Start time of amikacin from start time of earliest IV antibiotic taken Use the latest start time of antibiotic before of study drug. If IV antibiotic start time is missing, the time is not imputed. (Slot to ≥24 hours) For partial start time of antibiotic, impute to later of start time of study drug, hh:59 minute (if minute is missing), 23:mm (if hour is missing). For missing or partial start time of amikacin, use the earliest time possible for the start date: 00:00 if hour is missing; hh:00 is minute is missing.	• 0 to <12 hours • 12 to <24 hours • > 24 hours	a) Descriptive statistics b) Survival c) Pneumonia-related mortality d) Early clinical response e) Vent days f) ICU days

MDR designation

- To be declared a MDR, a bacterial isolate must be resistant to at least 3 (3 or more) of the 6 drug classes on the susceptibility panel below. Resistance must be to 3 or more drug classes from the same isolate at the same visit.

- Once a patient has any MDR pathogen, he/she should be designated as a MDR patient no matter what the subsequent susceptibility tests show.

- There can be 3 classes of patients based on MDR and timing of first detection of MDR in a patient:

  o MDR first detected at baseline

  o MDR first detected post baseline

  o Not MDR

- For the 3 cephams, resistance to any one of the 3 drugs in the panel counts as cepham resistance for the category.

- For consistency, consider a "NA" result as a "susceptible" for purposes of MDR tabulation. This means that 3+ results of "intermediate" or "resistant" are needed for MDR designation, and a "NA" does not count towards this total.

- CCLS interpretation of drug resistance will be used to determine MDR.

The efficacy table format would then be showing the primary endpoint and the 4 secondary endpoints for these 3 patient groups.

The modified listing for classifying MDR gram negatives should count intermediates as "non-susceptible"; therefore for the gram negatives the following criteria are used (with the addition of Levofloxacin as the quinolone). Previously, only true resistance designations were counted; the census is to also count the intermediates as "resistant" Adjustments are highlighted; drugs with an intermediate designation had that value moved into the resistant column.

Table 9–2 MDR designation

Drug Class	Drugs in panel	Resistance criteria	Susceptible
Aminoglycoside	Amikacin (AN)	32, 64, 128, 256	**16,8,4,…0.12**
β-lactam/β-lactamase inhibitor	Amox/Clav (AmC)	16/8, 32/16, 64/32	**8/4, ….<=0.03/ 0.015**
Cephams	Ceftazidime. (CAZ)	8, 16, 32, 64	**4,2,…</= 0.03**
	Cefazolin, (CZ)	32, 64	**16,8,4…</= 0.03**
	Cefpodoxime (CPD)	4, 8, 16, 32, 64	**2,1…</= 0.03**
Carbapenam	Imipenem (IPM)	2, 4, 8, 16, 32	**1,0.5,…</= 0.015**
Tetracycline	Tetracycline (TE)	8, 16, 32, 64	**4,2,…</= 0.03**
Folate pathway inhibitor	Trimethoprim-sulfamethoxazole (SXT)	4/76, 8/152, 16/304, 32/608	**2/38, 1/19, …..</=0.03/0.6**
Quinolone	Levofloxacin	4,8,16…	**2,1,0.5**

9.2   Appendix B: Definition of organ failure

The preferred terms "Organ failure" under MedDRA version 20.0 are:

Table 9–3 Preferred terms for "organ failure" under MedDRA v20.0

Preferred term (aeptnam)	PT code (aeptcd)
Multiple organ dysfunction syndrome	10077361
Acute on chronic liver failure	10077305
Acute left ventricular failure	10063081
Acute right ventricular failure	10063082
Cardiac failure	10007554
Cardiac failure acute	10007556
Cardiac failure congestive	10007559
Cardiogenic shock	10007625
Cardiopulmonary failure	10051093
Cardiorenal syndrome	10068230
Cor pulmonale acute	10010969
Left ventricular failure	10024119
Low cardiac output syndrome	10024899
Ventricular failure	10060953
Acute hepatic failure	10000804
Hepatorenal failure	10019845
Hepatorenal syndrome	10019846
Subacute hepatic failure	10056956
Septic shock	10040070
Toxic shock syndrome	10044248
Acute kidney injury	10069339
Renal failure	10038435
Acute respiratory failure	10001053
Respiratory failure	10038695
Circulatory collapse	10009192
Distributive shock	10070559
Hypovolaemic shock	10021138
Neurogenic shock	10058119
Shock	10040560
Shock haemorrhagic	10049771
Respiratory arrest	10038669
Acute respiratory distress syndrome	10001052
Hepatic encephalopathy	10019660
Purpura fulminans	10037556
Hepatic necrosis	10019692
Brain injury	10067967
Encephalopathy	10014625

Preferred term (aeptnam)	PT code (aeptcd)
Coma	10010071
Coma hepatic	10010075
Coma acidotic	10049037
Coma uraemic	10010082
Pancreatic failure	10079281
Cardiac arrest	10007515
Cerebral circulatory failure	10008097
Hepatic failure	10019663
Organ failure	10053159
Peripheral circulatory failure	10034567
Right ventricular failure	10039163
Postoperative renal failure	10056675

9.3   Appendix C: Definition of bronchial hyperreactivity

MedDRA HLT: Bronchospasm and obstruction

The preferred terms with primary or secondary path through MedDRA HLT "Bronchospasm and obstruction" under MedDRA version 19.1 are:

PT: Acute post asthmatic amyotrophy
PT: Airway remodelling
PT: Aspirin-exacerbated respiratory disease
PT: Asthma
PT: Asthma exercise induced
PT: Asthma late onset
PT: Asthma-chronic obstructive pulmonary disease overlap syndrome
PT: Asthmatic crisis
PT: Bronchial hyperreactivity
PT: Bronchial obstruction
PT: Bronchial oedema
PT: Bronchitis chronic
PT: Bronchospasm
PT: Bronchospasm paradoxical
PT: Bronchostenosis
PT: Chronic obstructive pulmonary disease
PT: Cystic fibrosis
PT: Cystic fibrosis lung
PT: Infantile asthma
PT: Infective exacerbation of chronic obstructive airways disease
PT: Infective pulmonary exacerbation of cystic fibrosis
PT: Obliterative bronchiolitis
PT: Obstructive airways disorder
PT: Occupational asthma
PT: Reactive airways dysfunction syndrome
PT: Reversible airways obstruction
PT: Severe asthma with fungal sensitisation
PT: Status asthmaticus
PT: Unilateral bronchospasm
PT: Wheezing

9.4 Appendix D: Definition of toxic-septic shock conditions

[SMQ] Toxic-septic shock conditions (SMQ)[V20]
PT: Acute kidney injury
PT: Acute prerenal failure
PT: Acute respiratory failure
PT: Anuria
PT: Blood pressure immeasurable
PT: Cerebral hypoperfusion
PT: Circulatory collapse
PT: Distributive shock
PT: Endotoxic shock
PT: Grey syndrome neonatal
PT: Hepatic congestion
PT: Hepatojugular reflux
PT: Hepatorenal failure
PT: Hypoperfusion
PT: Jugular vein distension
PT: Myocardial depression
PT: Neonatal anuria
PT: Neonatal multi-organ failure
PT: Neonatal respiratory failure
PT: Organ failure
PT: Prerenal failure
PT: Propofol infusion syndrome
PT: Renal failure
PT: Renal failure neonatal
PT: Respiratory failure
PT: Septic shock
PT: Shock
PT: Shock symptom
PT: Toxic shock syndrome