Supplemental Material

This was an open-label study with 1:1 randomization between two active treatment groups.

**Group 1:** Subjects received IV meropenem (2 g infused over 3 hrs q 8 hr) plus a parenteral aminoglycoside (tobramycin or gentamicin-5mg/kg IV Q24h or amikacin 20 mg/kg IV Q24h) plus tobramycin nebulization.

**Group 2 (Control arm):** Subjects received IV meropenem (2 g infused over 3 hrs q 8 hr).

Linezolid or vancomycin (per institutional guidelines) was available for MRSA coverage to subjects in either group.

The study population consisted of hospitalized male and female subjects ≥ 18 years with culture-documented hospital-acquired bacterial pneumonia (HABP); health-care associated pneumonia (HCAP) requiring mechanical ventilation; or ventilator-associated bacterial pneumonia (VABP). Subjects included those in any patient health care facility who developed pneumonia 72 or more hours after admission and those in a nursing home or rehabilitation center who developed pneumonia and were transferred to an acute care facility.

Male and female subjects ≥ 18 years with culture-documented pneumonia (i.e. HABP, HCAP or VABP) requiring mechanical ventilation were enrolled. Hospitalized subjects included those in any patient health care facility who develop pneumonia 72 or more hours after admission and those in a nursing home or rehabilitation center who develop pneumonia and were transferred to an acute care facility.

All subjects were stratified at randomization for APACHE II scores ≤18, >18 and use of steroids/immunosuppressive agents (YES, NO). Steroid/immunosuppressive agent use was defined as YES, if a subjects received >40 mg of prednisone or equivalent per day for a minimum of 14 days OR those subjects who received <40 mg of prednisone or equivalent per day PLUS another immunosuppressive agent (e.g. cyclosporine or others) for a minimum of 30 days. Subjects were randomized to one of two groups of active therapy or were classified as empiric non-qualifiers and followed for clinical outcome.

A subject’s eligibility for study inclusion was determined by the investigator prior to the initial bronchoscopic procedure and before the study treatment started. Subjects with non-diagnostic quantitative BAL cultures (<10^4 cfu/ml of BAL fluid) but with qualitative growth of an expected pulmonary pathogen from the pretreatment culture and with one or more positive pretreatment blood cultures, was considered eligible for group assignment and evaluation if the blood isolate was the same as that obtained from the respiratory culture. In this circumstance, evaluation for pretreatment pathogen response was based on the follow-up blood cultures AND follow-up respiratory cultures. Subjects not meeting these requirements were considered ineligible for the primary endpoint population.
All subjects who signed the approved informed consent were considered enrolled in the study and assigned a subject number. The site maintained a log of subjects enrolled in the study but did not qualify for group assignment.

For inclusion in the study, subjects fulfilled following criteria

1. Provision of written informed consent by the subject or subject’s legal representative.

2. Hospitalized males or females, 18 years or older, with respiratory failure requiring mechanical ventilation and clinical suspicion of HABP, HCAP or VABP.

3. Onset or exacerbation of pneumonia at least 48 hours after admission to any health care facility or onset of pneumonia in a nursing home or rehabilitation facility with subsequent transfer to an acute care facility (HCAP definition: and as defined in Inclusion criteria 6, 7, and 8). If the patient had pneumonia and met eligibility, the patient was enrolled. Once cultures were returned, the patient remained enrolled OR was dropped.

4. Women of childbearing potential were entered if their pregnancy test (urine or serum) was negative; they were instructed to abstain from sexual intercourse for the duration of the study or contraceptive measures were used until all follow-up procedures were completed.

5. Subjects who received previous antibacterial therapy within 14 days of pre-treatment bronchoscopy entry were entered only if the subject had not responded clinically (as defined in Inclusion Criteria 6, 7, and 8). Note: while less than 24 hours of pre-treatment antibiotics was preferential, recovery of $>10^4$ CFU/ml in the quantitative Bronchoscopic BAL was perceived as primary evidence that the prior therapy was not efficacious and enrollment was allowed.

6. Patients should have the following clinical findings that support a diagnosis of HABP/VABP/HCAP:

   a. Documented fever, defined as an oral or tympanic temperature greater than or equal to 38.0 degrees Celsius (100.4 degrees Fahrenheit), or a core temperature greater than or equal to 38.3 degrees Celsius (101 degrees Fahrenheit) or hypothermia, defined as a core body temperature of less than 35 degrees Celsius (95.2 degrees Fahrenheit); axillary temperatures are not recommended. Absence of fever was allowed in patients who meet all inclusion criteria with the exception of temperature. Elevated Procalcitonin may act as a marker substituting for fever or elevated white count.

   b. An elevated total peripheral white blood cell (WBC) count (WBC greater than 10,000/mm$^3$); or greater than 15 percent immature neutrophils (bands), regardless of total peripheral WBC count; or leukopenia with total WBC less than 4,500/mm$^3$.

   c. New onset of expectorated or suctioned respiratory secretions characterized by purulent appearance indicative of bacterial pneumonia.

In addition, patients with HABP should have at least one of the following present at enrollment:
• A new onset of cough (or worsening of baseline cough) during 48 or more hours of hospitalization or within 7 days after discharge from a hospital.

• Auscultatory findings on pulmonary examination of rales and/or evidence of pulmonary consolidation (e.g., dullness on percussion, bronchial breath sounds, or egophony).

• Dyspnea, tachypnea, or respiratory rate greater than 30/minute, particularly if any or all of these signs or symptoms are progressive in nature:

• Hypoxemia (e.g., a partial pressure of oxygen less than 60 mm Hg while the patient is breathing on room air as determined by arterial blood gas or oxygen saturation less than 90 percent while the patient is breathing on room air as determined by pulse oximetry, or worsening of the ratio of the partial pressure of oxygen to the fraction of inspired oxygen (PaO2/FiO2), respiratory failure requiring mechanical ventilation).

7. Radiographic Findings: Within 48 hours before starting empiric therapy a subject’s chest radiograph should show the presence of a NEW or progressive infiltrate, cavitation, or effusion suggestive of pneumonia.

8. Microbiologic Findings: Within 36 hours before the start of empiric study therapy, a quantitative culture of Bronchoscopic BAL fluid was obtained. Patients receiving standard-of-care therapy were eligible if their BAL had $\geq 10^4$ CFU/ml in their culture. In this case, monotherapy of all sorts is allowed (within 36 hours). To remain eligible, multiple antibiotic therapy may have been instituted provided at least one gram negative pathogen was resistant to all but one of the administered agents and the BAL had $> 10^4$ CFU/ml.

9. Patients with VABP must have had a Clinical Pulmonary Infection Score of $\geq 5$ and at least one of the following present at enrollment:
   • Auscultatory findings on pulmonary examination of rales and/or evidence of pulmonary consolidation.
   • Acute changes made in the ventilator support system to enhance oxygenation as determined by arterial blood gas or worsening PaO2/FiO2.

10.DEFINITIONS for ventilator-associated bacterial pneumonia (VABP):
   a. Definite VABP: Microbiological diagnosis based on quantitative culture of Bronchoscopic BAL ($\geq 10^4$ CFU/ml).
   b. Probable VABP: Clinical diagnosis based on a new and persistent radiographic infiltrate plus qualifying clinical signs as noted above in number 6 for HABP.
   c. Suspected VABP: Clinical suspicion of VABP triggering quantitative culture. Based on new radiographic infiltrate plus qualifying clinical signs, or any physician suspicion of VABP.
Any of the following was regarded as a criterion for EXCLUSION from the study:

1. Subjects with pneumonia caused by pathogens resistant to meropenem (MIC $>16$μg/ml) or a prior meropenem therapy failure.

2. Subjects with contra-indications to ANY study medication in particular with known or suspected allergy or hypersensitivity. This was inclusive of type I hypersensitivity to cephalosporins, penicillins, monobactams, carbapenems, and to vancomycin or linezolid.

3. Women who were pregnant or lactating.

4. Subjects on anticonvulsant medications for a known seizure disorder.

5. Subjects with known or suspected community acquired bacterial pneumonia (CABP) or viral pneumonia; subjects with acute exacerbation of chronic bronchitis without evidence of pneumonia.

6. Subjects with primary lung cancer or another malignancy metastatic to the lungs.

7. Subjects who were previously enrolled in this study.

8. Subjects who had an investigational drug or have used an investigational device within 30 days prior to entering the study.

9. Subjects with another focus of infection requiring concurrent antibiotics (e.g. other broad spectrum agents or those agents providing gram negative coverage) that would interfere with evaluation of the response to study drug.

10. Subjects with cystic fibrosis, acquired immune deficiency syndrome (AIDS) with a CD4 lymphocyte count $<200$ cells/μl, neutropenia (absolute neutrophil count $<500$ cells/ml), known or suspected active tuberculosis.

**NOTE:** Subjects taking steroids or immunosuppressive therapy were considered for enrollment. For purposes of stratification at randomization, subjects were considered YES for steroid/immunosuppressive use if they received 40 mg or more of prednisone or equivalent per day for a minimum of 14 days OR those subjects who received $<40$ mg of prednisone or equivalent per day PLUS another immunosuppressive agent (such as cyclosporine) for a minimum of 30 days. If patients did not meet these criteria, they are NO for steroid/immunosuppressive use.

11. Subjects with little chance of survival for the duration of study therapy (7-14 days) because of antecedent illness or underlying comorbidities.

12. Subjects with an APACHE II score $>35$.

13. Subjects with underlying condition(s) which would make it difficult to interpret response to the study drugs.
14. Subjects with hypotension (systolic BP of < 85mmHg) or acidosis (arterial pH < 7.25 or serum bicarbonate < 15 mg/dl) despite attempts at fluid resuscitation. Subjects who required ongoing treatment with vasopressors were eligible for the study if their hypotension was controlled and acidosis had resolved. Subjects with intractable septic shock were not eligible for enrollment.

15. Subjects who had a bone marrow transplantation.

16. Subjects with profound hypoxia as defined by a PaO₂/FiO₂ ratio < 100.