SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: MERREM™

ACTIVE INGREDIENT: meropenem

Trial title (number): A Multicenter, Randomized, Open-label Trial of MERREM™ I.V. (meropenem, ICI 194,660) and PRIMAXIN® I.V. (imipenem/cilastatin) for the Treatment of Community-acquired Bacterial Pneumonia (3591US/0022)

Clinical phase: IIIb

First patient recruited: 11 June 1998
Last patient completed: 19 June 2000
AstraZeneca approval date: 3 March 2001

Principal investigator and location (center number):

Publications/Presentations: None at the time of report preparation

OBJECTIVES: To acquire data from additional patients to evaluate the efficacy and safety of intravenous meropenem compared with imipenem/cilastatin for the treatment of community-acquired pneumonia (CAP). Secondary objectives (identified by a protocol amendment) were to measure meropenem plasma concentration levels in a subset of patients in order to: determine the pharmacokinetics of meropenem; determine the percentage of the dosing interval for which the plasma levels are above the minimum inhibitory concentration (MIC) levels of common CAP pathogens; and investigate the pharmacokinetic/pharmacodynamic relationship between meropenem plasma concentration levels and clinical or microbiological outcomes.

METHODS

Design: The trial was a multicenter, randomized, parallel-group, open-label trial. An independent, 3rd-party evaluator, who was blinded to treatment assignment, reviewed all case report forms after trial completion to confirm patient evaluability and response.

Population: Approximately 250 male and female patients with presumptive evidence of pneumonia at the time of admission to an acute-care facility or who developed pneumonia within 72 hours after admission were sought for enrollment in the trial, to provide 80 to 100 fully evaluable patients (40 to 50 per treatment group). Patients who were fully evaluable had to have clinically, radiologically, and microbiologically confirmed community-acquired bacterial pneumonia and to meet other evaluability criteria. This number of patients was based on the FDA request for additional experience with meropenem in patients with community-acquired pneumonia; determination of sample size was not based on power calculations of the number of patients required to demonstrate equivalence of treatment arms in this trial but rather the request of the FDA for 40 additional fully evaluable meropenem-treated patients.

Approximately 32 patients without renal impairment were expected to take part in the pharmacokinetic portion of the trial, to provide 24 evaluable patients for pharmacokinetic analysis.

Key inclusion criteria: Hospitalized patients 13 years of age or older with microbiologic, clinical, and radiographic evidence of pneumonia; signed informed consent provided by the patient, parent, or legal guardian; isolation of pretreatment pathogen(s) susceptible to the trial drug to which the patient was randomized. CAP was defined as pneumonia present at the time of admission to an acute-care facility or pneumonia that developed within 72 hours of hospitalization, and was not related to a prior admission to a healthcare facility. Patients who had received prior antimicrobial therapy for more than 24 hours could be entered if the pathogen was resistant to previous therapy or if a persistent positive culture was documented and the patient had not responded clinically.

Key exclusion criteria: Known bronchial obstruction or history of postobstructive pneumonia; primary lung cancer or another metastatic malignancy to the lungs; cystic fibrosis, human immunodeficiency virus (HIV), acquired immune deficiency syndrome, or active tuberculosis

Dosage: Eligible patients were randomly assigned to receive either meropenem 500 mg every 8 hours or imipenem/cilastatin 500 mg every 6 hours. Dosages of both drugs were to be reduced for patients with impaired renal function, according to the respective product labelling (recommended creatinine clearance cutoff value for dosage adjustment <51 ml/min for meropenem, <70 ml/min for imipenem/cilastatin). Doses of meropenem were administered intravenously by infusion over a 15- to 30-minute period; doses of imipenem/cilastatin were administered intravenously by infusion over a 20- to 30-minute period. The recommended treatment duration was 5 to 10 days depending on the patient's response. Based on the investigator's discretion, intravenous trial drug therapy could be changed to an oral antimicrobial agent after a minimum of 72 hours of intravenous treatment according to a predefined set of switching criteria.

Key assessments: Before treatment, patients were assessed for clinical, radiologic, and microbiologic (Gram stain) evidence of bacterial pneumonia. In addition, respiratory secretions and blood were cultured for pathogen isolation, identification, and susceptibility testing. During treatment, daily clinical signs and symptoms, and adverse events, withdrawals because of

adverse events, and deaths were recorded. At the end of randomized trial treatment, clinical laboratory, microbiologic, and follow-up radiologic assessments were performed. Overall clinical and microbiologic responses were assessed at the end of randomized trial treatment and 7 to 14 days (up to 28 days was allowed) after completion of all antimicrobial treatment. At the end of iv treatment, clinical response was judged as satisfactory (cure or improvement), unsatisfactory (failure), or indeterminate; at follow-up, clinical response was judged as satisfactory (cure), unsatisfactory (failure or relapse), or indeterminate. At end of iv treatment, microbiologic response was judged as satisfactory (eradication, presumed eradication, colonization), unsatisfactory (documented persistence, presumed persistence, or superinfection), or indeterminate. At follow-up, microbiologic response was judged as satisfactory (eradication, presumed eradication, colonization), unsatisfactory (recurrence, reinfection), or indeterminate.

Statistical considerations: The primary assessment of efficacy was based on the population of patients who were evaluable both clinically and microbiologically (fully evaluable, FE). In addition, assessments were conducted including patients who were evaluable clinically but not microbiologically (clinically evaluable, CE). Efficacy analyses were conducted for FE and CE patients in 2 populations (Analysis A and Analysis B). Analysis A included patients considered evaluable by the 3rd-party evaluator; however, because some patients considered evaluable in Analysis had major protocol deviations, an additional analysis was performed. This analysis is referred to as Analysis B and included patients deemed evaluable by the Sponsor based on computer identification of protocol deviations and review by the study team physician without knowledge of treatment assignment. In addition, an intention-to-treat (ITT) analysis was performed, which included all patients who were given trial treatment.

The primary efficacy measure was clinical response at follow-up (7 to 14 days after completion of all antimicrobial treatment [up to 28 days was allowed]). Secondary measures were clinical and microbiologic responses at the end of randomized trial therapy and microbiologic response at follow-up. The proportion of evaluable patients with satisfactory responses for each of these 4 end points was summarized. The treatment difference (meropenem – imipenem/cilastatin) for the proportion of patients with a satisfactory response and the associated 95% confidence interval (CI) was constructed.

Adverse event and clinical laboratory data were summarized for all patients who received at least 1 dose of trial medication.

RESULTS

Demography: A total of 287 patients from 22 centers in the United States were randomized to treatment with either iv meropenem (N=144) or iv imipenem/cilastatin (N=143). Six of the 287 randomized patients (4 meropenem, 2 imipenem/cilastatin) were withdrawn from the trial before beginning trial treatment, and 281 were given trial treatment (139 meropenem, 142 imipenem/cilastatin). Three of the 281 patients were given the wrong trial drug: 2 were randomized to meropenem but given imipenem/cilastatin; and 1 was randomized to imipenem/cilastatin but given meropenem. These patients are excluded from the primary efficacy analyses, and included in ITT and safety analyses according to treatment received. The number of evaluable patients in Analysis A and Analysis B populations are summarized in Table I.

Table I Summary of evaluable patient populations

Evaluability	Analysis A population[a]		Analysis B population[b]	
	Meropenem	Imipenem/ cilastatin	Meropenem	Imipenem/ cilastatin
Fully evaluable (clinically and microbiologically)	60	58	58	59
Clinically evaluable[c]	93	91	88	87
Unevaluable[d]	46	51	51	55
All patients	139	142	139	142

[a] Evaluability for Analysis A is determined by the 3rd-party evaluator's assessment.
[b] Evaluability for Analysis B is based on computer identification of protocol deviations and evaluation by the project physician without knowledge of treatment assignment.
[c] Includes fully evaluable patients and patients who were clinically evaluable only.
[d] Patients who were not clinically evaluable.

Overall, the population of all patients treated was predominantly elderly (58% of patients were 65 years of age or older; mean age 65 years), predominantly male (65%), and predominantly white (75%). Nearly half of the patients (48%) had reduced creatinine clearance (defined as <60 ml/min) at baseline, nearly one-third (31%) had underlying pulmonary disease (as defined by chronic bronchitis, emphysema, or bronchiectasis), and 36% had a history of prior pneumonia. The majority of patients (78%) switched to an oral antibiotic after receiving a median of 5 days of iv trial treatment, and received oral treatment for a median of 8 days. Follow-up occurred a median of 9 days after the end of all antibiotic treatment (iv or oral). Among all patients treated, the treatment groups were generally well balanced with respect to demographic and baseline characteristics, although a slightly higher proportion of meropenem-treated patients had a history of asthma, emphysema, and current alcohol use; and a slightly higher proportion of imipenem/cilastatin-treated patients had a history of prior pneumonia, congestive heart failure, and diabetes mellitus. Differences between treatment groups with respect to demographic and baseline characteristics were seen among fully evaluable patients in Analysis A and also among clinically evaluable patients in Analysis B. In the fully evaluable meropenem group in Analysis A, more patients had medical histories with key significant comorbidities compared to imipenem/cilastatin patients, eg, asthma 22% vs 12%; emphysema 28% vs 14%, prior pneumonia 35% vs 24%, alcohol use 25% vs 19%, underlying pulmonary disease at baseline (bronchitis, emphysema, or bronchiectasis) 33% vs 21%, respectively. Furthermore, 40% of meropenem patients were greater than 75 years of age, compared to 28% of imipenem/cilastatin patients, and more patients in the meropenem group had reduced baseline creatinine clearance values (<60 ml/min) compared to the imipenem/cilastatin group (55% versus 43%).

Pharmacokinetics: A series of plasma samples for meropenem analysis were obtained from 7 nonrenally impaired patients treated at 1 center. Samples were obtained following repeated dosing (after at least 4 doses of meropenem 500 mg iv every 8 hours) and at specified time points relative to a 30-minute intravenous infusion of 500 mg of meropenem. Two of the 7 patients were excluded from the analysis of the plasma meropenem profiles because of

apparent labelling errors on sample tubes. The plasma concentration profile for 1 patient in the present trial was in the expected range for the 500-mg meropenem dose (based on results of a published single-dose study in healthy volunteers), while the profiles for the remaining 4 patients were slightly higher than the 95% confidence interval range for results from the previous trial. The higher plasma concentration-time profiles noted in the present trial may be related to the demographic characteristics of the patients (age range of the 5 volunteers in the published trial was 20 to 39 years, compared to an age range of 45 to 68 years for the 5 patients in the present trial).

Plasma concentrations following the 500-mg meropenem doses given in the present trial ranged from 0.75 to 8.6 mcg/ml at the last time point of 4.5 hours after the start of drug infusion (a period covering 56% of the dosing interval).

At the end of the meropenem treatment period, 6 of the 7 patients that participated in the pharmacokinetic evaluations had either a clinical response of cured or improved (1 patient did not have a clinical response assessed).

These results indicate that adequate plasma levels of meropenem following repeated 500-mg doses are obtained to treat organisms that are common causes of community-acquired pneumonia.

Efficacy: The primary assessment of efficacy was clinical response at follow-up in the fully evaluable population. Table II presents clinical response at follow-up for fully evaluable and clinically evaluable patients in Analysis A, Analysis B, and the ITT analysis.

Table II Satisfactory clinical responses at follow-up

Satisfactory clinical response at follow-up[a], number (%) of patients	Meropenem		Imipenem/cilastatin	
	Fully evaluable	Clinically evaluable	Fully evaluable	Clinically evaluable
Analysis A	N=60[b] 49 (86.0)	N=93[b] 76 (86.4)	N=58 56 (96.6)	N=91[b] 85 (94.4)
Analysis B	N=58 54 (93.1)	N=88 73 (83.0)	N=59 56 (94.9)	N=87 79 (90.8)
ITT analysis	N=139 88 (63.3)		N=142 100 (70.4)	

[a] Satisfactory clinical response is defined as cure or improvement.

[b] Patients who had no assessment done are not included in the denominator for satisfactory response.

N Number of patients in population.

Differences in clinical response between meropenem and imipenem/cilastatin patients in Analysis A and in clinically evaluable patients from Analysis B may be explained by 2 important observations. First, population asymmetry was present between treatment groups (except for fully evaluable patients in Analysis B, where differences in demographic comorbidities between the treatment arms were less notable). In Analysis A, more meropenem patients had significant comorbidities present at baseline compared to imipenem/cilastatin patients (as noted above), and failures tended to occur in patients who had significant comorbidities. Comorbidities such as these have been reported to be associated with an increased risk of adverse outcome in patients

with CAP (Fine et al 1997). Secondly, all meropenem patients who had unsatisfactory clinical responses had 5 or fewer days of iv treatment. When patients were treated for more than 5 days, Analysis A shows that 100% of meropenem patients (fully and clinically evaluable patients) were clinical successes at follow-up compared to 96% of fully evaluable and 94% of clinically evaluable imipenem/cilastatin patients. In Analysis B, 91% of fully evaluable patients treated for more than 5 days were clinical successes in both the meropenem arm and the imipenem/cilastatin arm. Similarly in the ITT analysis, when patients were treated for more than 5 days, 76% of meropenem patients and 79% of imipenem/cilastatin patients were clinical successes at follow-up.

Secondary efficacy assessments include clinical response at end of treatment, and microbiologic response at end of treatment and follow-up. As shown in Tables III and IV, satisfactory response rates were generally similar between treatment groups in each analysis for end of treatment clinical response and for microbiologic response at end of treatment and follow-up.

Table III Satisfactory clinical response at end of treatment

Satisfactory clinical response at end of treatment[a], number (%) of patients	Meropenem		Imipenem/cilastatin	
	Fully evaluable	Clinically evaluable	Fully evaluable	Clinically evaluable
Analysis A	N=60[b] 56 (96.6)	N=93[b] 87 (95.6)	N=58 58 (100)	N=91[b] 89 (98.9)
Analysis B	N=58 56 (96.6)	N=88 82 (93.2)	N=59 58 (98.3)	N=87 85 (97.7)
ITT analysis	N=139 112 (80.6)		N=142 116 (81.7)	

[a] Satisfactory clinical response is defined as cure or improvement.
[b] Patients who had no assessment done are not included in the denominator for satisfactory response.
N Number of patients in population.

Table IV Satisfactory microbiologic response at end of treatment and follow-up

Satisfactory microbiologic response[a], number (%) of patients	Meropenem		Imipenem/cilastatin	
	End of treatment	Follow-up	End of treatment	Follow-up
Analysis A - ‘fully evaluable patients	N=59[b] 57 (96.6)	N=53[b] 51 (96.2)	N=57[b] 56 (98.2)	N=57[b] 57 (100)
Analysis B - fully evaluable patients	N=58 57 (98.3)	N=58 55 (94.8)	N=59 57 (96.6)	N=59 57 (96.6)
ITT analysis	N=139 81 (58.3)	N=139 62 (44.6)	N=142 72 (50.7)	N=142 66 (46.5)

[a] Satisfactory microbiologic response is defined as eradication, presumed eradication, or colonization.
[b] Patients who had no assessment done are not included in the denominator for satisfactory response.
N Number of patients in population.

Satisfactory response rates for pretreatment pathogens were generally similar between the meropenem group and the imipenem/cilastatin group in each population (Table V). The number of individual pretreatment pathogens isolated was similar between treatment groups, except in the ITT population where a greater number of meropenem-treated patients had *S. pneumoniae* isolated compared to the imipenem/cilastatin arm (42 versus 28 patients).

Table V Satisfactory response rates for pretreatment pathogens

Satisfactory response[a], n/N (%)	Analysis A - fully evaluable patients		Analysis B - fully evaluable patients		ITT analysis	
	Meropenem	Imipenem/ cilastatin	Meropenem	Imipenem/ cilastatin	Meropenem	Imipenem/ cilastatin
Gram-positive aerobes						
Staphylococcus aureus	7/7 (100)	4/4 (100)	6/6 (100)	5/6 (83.3)	9/9 (100)	6/7 (85.7)
Streptococcus pneumoniae	28/29 (96.6)	20/20 (100)	30/30 (100)	23/23 (100)	41/42 (97.6)	28/28 (100)
Gram-negative aerobes						
Branhamella catarrhalis	5/6 (83.3)	7/7 (100)	4/5 (80.0)	6/6 (100)	8/9 (88.9)	9/9 (100)
Enterobacter aerogenes	0	2/2 (100)	0	2/2 (100)	0	2/2 (100)
Escherichia coli	2/2 (100)	3/3 (100)	2/2 (100)	2/2 (100)	3/3 (100)	5/5 (100)
Haemophilus influenzae	16/17 (94.1)	16/16 (100)	17/18 (94.4)	19/19 (100)	23/24 (95.8)	21/21 (100)
Haemophilus parainfluenzae	1/1 (100)	3/3 (100)	2/2 (100)	3/3 (100)	3/3 (100)	4/4 (100)
Klebsiella pneumoniae	3/3 (100)	3/3 (100)	1/1 (100)	3/3 (100)	3/3 (100)	3/3 (100)
Pseudomonas aeruginosa	1/2 (50.0)	1/1 (100)	2/3 (66.7)	0	3/4 (75.0)	1/1 (100)
Serratia marcescens	2/2 (100)	2/2 (100)	1/1 (100)	2/2 (100)	2/2 (100)	3/3 (100)

[a] Satisfactory response is defined as eradication or presumed eradication of the pretreatment pathogen.
N Number of patients with pretreatment pathogen; n Number of patients with satisfactory response.

In summary, differences in comorbidities at baseline coincided with differences in satisfactory response rates, with a greater proportion of fully evaluable meropenem-treated patients having risk factors for adverse outcomes compared to the imipenem/cilastatin group. In Analysis A, 86% of fully evaluable meropenem patients and 97% of imipenem/cilastatin patients had satisfactory clinical responses at follow-up; satisfactory microbiologic responses were similar between the treatment arms (96% and 100%, respectively). In Analysis B, 93% of fully evaluable meropenem patients and 95% of imipenem/cilastatin patients had satisfactory clinical responses at follow-up; satisfactory microbiologic responses were similar (95% and 97%, respectively) between the treatment arms. The satisfactory response rate observed for meropenem at follow-up is consistent with published studies of meropenem and other antibiotics as treatment for community-acquired pneumonia in high risk, hospitalized patients (Bartoloni 1999, Berman 1997, Pozzi, 1999, Romanelli 1995).

When patients were treated with iv therapy for more than 5 days, 91% to 100% of fully evaluable patients (Analyses A and B) in both treatment groups were clinical successes at follow-up; in the ITT population, 76% of meropenem patients and 79% of imipenem/cilastatin patients were clinical successes. When patients were treated for 5 days or less, the percentage of meropenem successes dropped to 78% in Analysis A and Analysis B and 57% in the ITT analysis, compared to 97% in Analysis A, 91% in Analysis B, and 66% in the ITT analysis for imipenem/cilastatin patients.

Safety: The total number of patients with 1 or more adverse events reported during the trial (regardless of attributed relationship to trial treatment) was similar in the 2 treatment groups (78% [109 of 139] for meropenem, 79% [112 of 142] for imipenem/cilastatin). Among meropenem-treated patients, the most common adverse events (% of patients) were diarrhea (12%), insomnia (10%), and headache (10%). Among patients given imipenem/cilastatin, the most common adverse events were headache (13%), nausea (12%), and peripheral edema (9%). Only 12% (16 of 139) of meropenem-treated patients and 15% (21 of 142) imipenem/cilastatin-treated patients had at least 1 adverse event that the investigator considered drug related. The most common drug-related adverse events in the meropenem group were diarrhea (2.9%) and increased ALT (1.4%), and in the imipenem/cilastatin group were nausea (3.5%), oral moniliasis (2.1%), diarrhea (1.4%), confusion (1.4%), and rash (1.4%). In addition to the 2 meropenem-treated patients (1.4%) with drug-related adverse events of increased ALT, 1 patient had a drug-related event of elevated liver enzymes; thus, the total incidence of drug-related adverse events related to elevated liver enzymes in the meropenem group was 2.2% (3 of 139 patients). One patient (0.7%) in the imipenem/cilastatin group had a drug-related adverse event related to elevation of liver function enzymes (increased AST).

Eight patients (5.8%) in the meropenem group and 7 (4.9%) in the imipenem/cilastatin group had an adverse event that led to trial withdrawal. In only 2 patients in each treatment group were the adverse events leading to withdrawal considered related to trial treatment: chest pain, burning sensation, feeling faint and flushed (meropenem); altered mental status (meropenem); headache and jaw pain (imipenem/cilastatin); nausea (imipenem/cilastatin). All of these events were nonserious events.

A total of 30 patients (22%) in the meropenem group and 24 patients (17%) in the imipenem/cilastatin group had 1 or more serious adverse events either during intravenous trial treatment or within 30 days after trial treatment ended. No patient in either treatment group had a serious adverse event of seizure. Included in the 54 patients with serious adverse events are 20 patients who died (13 meropenem, 7 imipenem/cilastatin). None of the deaths was considered related to trial treatment. The patients' primary pneumonia was considered to be a contributory factor (with other causes) in 5 of the 13 deaths in the meropenem group and 4 of 7 deaths in the imipenem/cilastatin group. For both treatment groups, the overall mortality rate (9% for meropenem, 5% for imipenem/cilastatin) is lower than the average mortality rate of 14% reported for hospitalized patients with CAP (Fine et al 1996).

Recurrent or worsening pneumonia was reported as an adverse event for 13 meropenem-treated patients and no imipenem/cilastatin-treated patients. In addition, 8 patients (2 meropenem, 6 imipenem/cilastatin) had an unsatisfactory clinical response (relapse or failure) at follow-up after having a satisfactory clinical response at end of iv treatment and pneumonia was not

reported as an adverse event, and 8 additional patients (3 meropenem, 5 imipenem/cilastatin) had another adverse event consistent with recurrent or persistent lower respiratory tract infection. Thus, a total of 18 meropenem-treated patients and 11 imipenem/cilastatin-treated patients had either an adverse event of pneumonia, an unsatisfactory clinical response at follow-up, or another adverse event consistent with recurrent or persistent lower respiratory tract infection (eg, lung abscess, empyema, COPD exacerbation). Nearly all of these patients (89% for meropenem, 82% for imipenem/cilastatin) had a history of preexisting pulmonary disease (including COPD, asthma, prior pneumonia).

For meropenem-treated patients with recurrent pneumonia events, the events generally occurred after a short course of iv therapy and well after a switch to oral antibiotics. More patients in the meropenem group who had recurrent pneumonia events received 5 days or less of iv treatment compared to the percentage in the imipenem/cilastatin group (83% versus 46%). The median duration of time to the recurrent pneumonia event from the end of iv trial treatment was 14 days for meropenem compared to 3 days for imipenem/cilastatin; thus, the events occurred late and appear to be related to early discontinuation of iv treatment and switch to oral antibiotic treatment rather than trial treatment.

Logistic regression analyses were performed to evaluate factors contributory to adverse outcomes of death, serious adverse events, and recurrent pneumonia events. Trial treatment (meropenem vs imipenem/cilastatin) and the presence of underlying chronic pulmonary disease (chronic bronchitis, bronchiectasis, or emphysema) were not significant predictors for serious adverse events as a whole, for deaths, or for recurrent pneumonia events. Reduced creatinine clearance at baseline (<60 ml/min) was a significant predictor of death and showed a trend towards significance as a predictor of serious adverse events; it was not a significant predictor for recurrent pneumonia events.

Results of the Mantel-Haenszel Chi square test and relative risk assessments for serious adverse events, deaths, and recurrent pneumonia events indicate that none of these outcomes demonstrated a significant difference between treatments.

No notable differences were seen between the 2 treatment groups in the proportion of patients with clinically defined laboratory changes. Seventeen patients (8 meropenem, 9 imipenem/cilastatin) had an increase in AST or ALT to more than 3 times the baseline value. Of the 17 patients, 8 (4 in each treatment group) had increases in either AST or ALT that were more than 5 times the baseline value, and 9 (4 meropenem, 5 imipenem/cilastatin) had increases that were more than 3 times but less than 5 times the baseline value. For 9 patients (6 meropenem, 3 imipenem/cilastatin) who had follow-up ALT or AST values obtained, all follow-up values showed either a return to baseline values or a marked improvement from the peak elevations.

Twenty-two (16%) meropenem-treated patients and 30 (21%) imipenem/cilastatin-treated patients had a clinically defined decrease in hemoglobin (at least 2.5 g/dl) or hematocrit (at least 8 vol %). Of these patients, 1 in the meropenem group and 3 in the imipenem/cilastatin group had an adverse event related to clinical bleeding, none of which was considered drug related by the investigators.

In summary, the safety profile of meropenem in hospitalized patients with CAP was similar to that of imipenem/cilastatin and there were no unexpected new safety issues. Although there was a higher number of deaths, recurrent pneumonia events, and serious adverse events in the

meropenem arm compared to the imipenem/cilastatin arm, regression analyses demonstrated that treatment assignment was not a predictor for the occurrence of these events. Despite the higher number of recurrent pneumonia events in the meropenem arm compared to the imipenem/cilastatin arm, these events appeared to be related to underlying pathology or early discontinuation of iv treatment and switch to oral antibiotic treatment rather than to trial treatment.