AstraZeneca

Drug product:	Meropenem	**SYNOPSIS**	
Drug substance(s):	Meropenem		
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A Multicenter, Randomized, Double-blind, Comparative Trial of Intravenous MERREM™ (meropenem, ICI 194,660) vs PRIMAXIN® I.V. (imipenem-cilastatin) in the Treatment of Hospitalized Subjects with Complicated Skin and Skin Structure Infections

International co-ordinating investigator

None

Study centers

This study was conducted at 75 centers in the United States and 8 centers in South Africa, 6 centers in Canada, and 3 centers in Brazil.

Publications

None at issue

Study dates		**Phase of development**
First patient enrolled	28 March 2001	Therapeutic confirmatory (III)
Last patient completed	10 December 2003	

Objectives

The primary objective of this study is to demonstrate the therapeutic noninferiority of meropenem (500 mg intravenous [iv] every 8 hours) to imipenem-cilastatin (500 mg iv every 8 hours) in hospitalized patients with complicated skin and skin structure infections.

The secondary objective of this study is to assess the safety and tolerability of meropenem (500 mg iv every 8 hours) administered in hospitalized patients with complicated skin and skin structure infections.

Study design

This was a multicenter, randomized, double blind, comparative study of iv meropenem and iv imipenem-cilastatin.

Target patient population and sample size

Approximately 1000 hospitalized male and female patients, aged 13 years or older, with clinical evidence of complicated skin and skin structure bacterial infection with material suitable for culture, were required to be randomized to study drug in order to acquire 201 clinically evaluable patients in each treatment group.

Investigational product and comparators: dosage, mode of administration, and batch numbers

AstraZeneca provided commercially labeled and packaged meropenem and imipenem-cilastatin. Meropenem powder, 500 mg/20-mL vial (batch numbers 3345C/ 2000012670, 3764C/ 2000012663, 8071F/ 2000034348, 8071F/ 2000030524, 8071F/ 2000033714, 8071F/ 2000042002, 5526J/ 2000044037, 5521J/ 2000045609); imipenem-cilastatin powder, 500 mg/10-mL vial (batch numbers 4475M/ 2000034712, 3631M/ 2000037946, 4304L/ 2000030525, 3811K/ 2000014524, 3573N/ 2000045611, 4445M/ 2000033762, 3703M/ 2000042003); and imipenem-cilastatin suspension, 500 mg/100 mL (batch number 3582K/ 2000012672) were administered by iv infusion over approximately 20 to 30 minutes. The dose and/or frequency of administration was adjusted from 500 mg every 8 hours according to creatinine clearance (>50mL/min for patients randomized to meropenem, >70 mL/min for patients randomized to imipenem-cilastatin).

Duration of treatment

The duration of iv study treatment was expected to be from 3 to14 days.

Criteria for evaluation (main variables)

Efficacy

- Primary variable: clinical outcome at the post-treatment follow-up visit
- Secondary variables:
  - clinical outcome at the post-treatment follow-up visit (excluding clinical outcomes assessed as co-primary variables)
  - clinical outcome at the end-of-treatment visit
  - microbiological outcome at the end-of-treatment and post-treatment follow-up visits
  - pretreatment pathogen outcome at the end-of-treatment and the post-treatment follow-up visits

- Additional heath economics variables:
  - total length of hospital stay
  - number of iv treatment doses
  - number of days of iv therapy
  - number of days of oral antibiotic therapy
  - number of intensive care unit bed days
  - number of days missed from work, school, and other activities since end of iv therapy

Safety

- incidence and severity of adverse events throughout the study
- incidence and severity of serious adverse events throughout the study
- incidence of discontinuations from the study attributed to adverse events
- laboratory parameters at the discretion of the investigator and at end-of-treatment and post-treatment follow-up visits

Statistical methods

The co-primary efficacy analysis was the study outcome with respect to the clinical response of the CE and MITT analysis sets at the post-treatment follow-up visit. Clinical noninferiority of the 2 treatments was determined if the lower bound of the 2-sided 95% confidence interval (CI) of the difference in outcomes of satisfactory between treatments (meropenem minus imipenem-cilastatin) in the CE analysis set was greater than –10% using the asymptotic normal approximation to the binomial distribution, without continuity correction, for the difference in proportions. Subgroup analyses were performed based on whether dosages were adjusted for renal function. The analysis of patients with dose adjustments based upon renal function (RDA) was considered a sensitivity analysis. Additional assessments were performed on the CE analysis set at the post-treatment follow-up visit subgrouped by primary infection diagnosis, age, gender, race, location of study center, diabetes mellitus, and initial surgical intervention. Concordance between clinical and microbiological outcomes at the post-treatment follow-up visit in the CE analysis set was also determined.

Secondary analyses were based on data obtained at end-of-treatment and post-treatment follow-up visits for patients in the analysis sets described below (excluding clinical outcomes assessed as co-primary variables): CE, MITT, intention-to-treat (ITT), microbiological ITT, microbiological MITT, and fully evaluable (FE). Methods and models were the same as for

the primary analysis, and were presented for all patients, patients with RDA, and patients with no adjustment in dosage for renal function (NRDA).

Patients were assigned to the following analysis sets:

Safety analysis set:	all patients who received at least 1 dose of study drug were assigned according to the treatment received
ITT analysis set:	all patients who received at least 1 dose of study drug were assigned according to the treatment randomized
Microbiological ITT analysis set:	all patients in the ITT analysis set with an identified pretreatment pathogen
MITT analysis set:	all patients in the ITT analysis set who were hospitalized with a complicated skin and skin structure infection and met all study inclusion and exclusion criteria
Microbiological MITT analysis set:	all patients in the MITT analysis set with an identified pretreatment pathogen
CE analysis set:	all patients in the MITT analysis set who fulfilled all predefined evaluability criteria
FE analysis set:	all patients in the CE analysis set with an identified pretreatment pathogen

Patient population

Of the 1076 patients randomized to study drug, 535 patients were randomized to receive meropenem and 541 were randomized to receive imipenem-cilastatin; 39 patients did not receive study drug. The safety analysis set contained 511 patients who received meropenem and 526 patients who received imipenem-cilastatin. The demographic and baseline characteristics of patients in each treatment group were similar (Table S1 and Table S2).

Table S1 Demographic characteristics (ITT analysis set)

Demographic characteristic		**Treatment group (n [%], unless noted)**	
		Meropenem N=510	**Imipenem-cilastatin N=527**
Sex (n , %)	Male	303 (59)	322 (61)
	Female	207 (41)	205 (39)

Table S1 Demographic characteristics (ITT analysis set)

Demographic characteristic		Treatment group (n [%], unless noted)	
		Meropenem N=510	**Imipenem-cilastatin N=527**
Age (years)	Mean (SD)	48.8 (16.2)	48.5 (17.2)
	Range	14 to 91	13 to 95
	13 to 16	3 (1)	3 (1)
	17 to 44	200 (39)	217 (41)
	45 to 64	215 (42)	213 (40)
	65 to 74	55 (11)	47 (9)
	≥75	37 (7)	47 (9)
Race (n, %)	White	239 (47)	253 (48)
	Black	135 (27)	143 (27)
	Asian	19 (4)	23 (4)
	Hispanic	56 (11)	50 (10)
	Other	61 (12)	58 (11)

SD Standard deviation.

The patient population was at risk for severe consequences of complicated skin and skin structure infections. Of patients included in the ITT analysis set (510 patients randomized to meropenem and 527 patients randomized to imipenem-cilastatin), 18% in each treatment group were older than 65 years, approximately 37% of patients had diabetes mellitus, and approximately 12% had peripheral vascular disease; 93% of patients in each treatment group had infections of moderate or severe intensities.

Approximately 23% of all patients in the ITT analysis set had at least 1 prior surgery related to skin and skin structure infection. More than 67% of patients in each treatment group required initial surgical intervention on the primary wound site at the time of study entry. Additionally, approximately 66% of all patients in the ITT analysis set had received prior antibiotics. Thus the enrolled population is broadly representative of the clinical patient population with complicated skin and skin structure infections one would expect to see in the United States.

Table S2 Baseline characteristics (ITT analysis set)

Baseline characteristic		Treatment group (n [%], unless noted)	
		Meropenem N=510	**Imipenem-cilastatin N=527**
Weight (kg)	Mean (SD)	85.2 (27.5)	87.9 (31.2)
	Range	40 to 204	35 to 308
	n	508	527
Smoking history (n, %)	Never	232 (46)	237 (45)
	Current	178 (35)	205 (39)
	Previous	99 (19)	82 (16)
	Missing	1 (<1)	3 (1)
Consumed more than 3 alcoholic drinks daily (n, %)	Yes	47 (9)	55 (10)
	No	462 (91)	469 (89)
	Missing	1 (<1)	3 (1)
General condition (n, %)	Good	219 (43)	225 (43)
	Fair	250 (49)	255 (48)
	Poor	40 (8)	44 (8)
	Critical	0	3 (1)
Current significant medical condition[a] (n, %)	Diabetes mellitus	195 (38)	183 (35)
	Arterial peripheral vascular disease	56 (11)	68 (13)
	Recurring cellulitis	45 (9)	40 (8)
	Chronic skin ulcers	38 (8)	46 (9)
	Congestive heart failure	34 (7)	43 (8)
	Venous stasis disease	22 (4)	33 (6)
Days since onset of symptoms	1 to 7	359 (71)	343 (65)
	8 to 14	87 (17)	107 (20)
	More than 14	52 (10)	58 (11)
	Missing	11 (2)	19 (4)

Table S2 Baseline characteristics (ITT analysis set)

Baseline characteristic		Treatment group (n [%], unless noted)	
		Meropenem N=510	**Imipenem-cilastatin N=527**
Infection diagnosis (n, %)	Complex abscess	212 (42)	219 (42)
	Wound infection	91 (18)	101 (19)
	Cellulitis	88 (17)	89 (17)
	Infected ischemic/ diabetic ulcer(s)	51 (10)	44 (8)
	Perirectal abscess	37 (7)	42 (8)
	Other	30 (6)	32 (6)
Primary infection source (n, %)	Community acquired	402 (79)	413 (78)
	Unknown	70 (14)	64 (12)
	Hospital/chronic	37 (7)	50 (10)
Primary infection cause (n, %)	Spontaneous	175 (34)	171 (32)
	Trauma	116 (23)	136 (26)
	Underlying medical condition	80 (16)	89 (17)
	Prior surgery	54 (11)	49 (9)
	Other	48 (9)	50 (10)
	Bite	36 (7)	32 (6)
Infection site (n %)	Single	471 (93)	482 (92)
	Multiple	38 (8)	45 (9)
Extent of infection (n, %)	Superficial	107 (21)	104 (20)
	Deep	402 (79)	423 (80)
Intensity of infection (n, %)	Mild	39 (8)	38 (7)
	Moderate	313 (62)	305 (58)
	Severe	157 (31)	183 (35)
	Missing	0	1 (<1)
Pretreatment medication (n, %)	Non-antibacterial drug	504 (99)	520 (99)
	Antibacterial drug	336 (66)	345 (66)

Table S2 Baseline characteristics (ITT analysis set)

Baseline characteristic		Treatment group (n [%], unless noted)	
		Meropenem N=510	**Imipenem-cilastatin N=527**
Pretreatment antibacterial medication[b] (n, %)	Cefazolin	93 (18)	103 (20)
	Sultamicillin (ampicillin/ sulbactam)	48 (9)	58 (11)
	Ceftriaxone	33 (7)	29 (6)
	Penicillin, nos	32 (6)	25 (5)
	Levofloxacin	31 (6)	28 (5)
	Cefalexin	26 (5)	37 (7)
Prior surgery related to skin structure infection[a] (n, %)	Any surgery	121 (24)	122 (23)
	Incision and drainage of wound	54 (11)	40 (8)
	Amputation	23 (5)	28 (5)
	Debridement	17 (3)	23 (4)
Initial surgical intervention on primary wound site (n, %)	Any surgery	346 (68)	368 (70)
	Incision and drainage of wound	275 (54)	278 (53)
	Operative debridement	71 (14)	84 (16)
	Other	34 (7)	52 (10)
	Amputation	11 (2)	6 (1)
	Wound closure	0	1 (<1)

[a] Experienced by at least 20 patients in either treatment group.
[b] Administered to more than 30 patients in either treatment group.
SD Standard deviation.
nos Not otherwise specified.

Among the pretreatment pathogens isolated from patients in the microbiological ITT analysis set, there were no relevant differences in *in vitro* susceptibility to meropenem and imipenem.

Efficacy results

The lower bound of the 95% CI of the difference in satisfactory clinical outcomes in the CE analysis set (meropenem minus imipenem-cilastatin) is –2.8, which is greater than that needed

to demonstrate the noninferiority of meropenem to imipenem-cilastatin in the treatment of patients with clinical evidence of complicated skin and skin structure bacterial infection. This result is supported by an analysis of clinical outcomes for patients in the MITT analysis set, which yields a corresponding lower bound of –8.4, and in the analyses of clinical outcomes for patients in the remaining analysis sets at the post-treatment follow-up and end-of-treatment visits. There are no clinically relevant differences between the results of the primary and secondary analyses. The noninferiority of meropenem to imipenem-cilastatin is supported in assessments of subpopulations categorized by dosage adjustment, initial surgical intervention, infection diagnosis, diabetes mellitus, patient age, gender, location of study center, and number of pretreatment pathogens.

Differences in the proportions of patients with successful microbiological outcomes in secondary analyses of the FE, microbiological MITT, and microbiological ITT support the results of the primary analysis of clinical outcome. Among the most common pretreatment pathogens isolated from at least 10 patients in the FE analysis set, there were no clinically relevant differences between treatment groups in the proportion of patients with clinically successful outcomes at either time of assessment. The most common pathogens isolated at least 10 times in patients randomized to meropenem were:

Gram-positive aerobes:	*Staphylococcus aureus*, methicillin susceptible; *Streptococcus pyogenes* (Group A); *Streptococcus agalactiae* (Group B); *Streptococcus viridans* Group, nos; and *Enterococcus faecalis*
Gram-negative aerobes:	*Escherichia coli*, *Pseudomonas aeruginosa*; Klebsiella species (*K. pneumoniae and K. oxytoca)*; and *Proteus mirabilis*
Gram-negative anaerobes:	*Bacteroides fragilis*

There were no clinically relevant differences between the proportion of patients with satisfactory pretreatment pathogen outcomes and corresponding proportions of patients with satisfactory clinical outcomes. The proportion of patients in the FE analysis set with concordant clinical and microbiological outcomes was similar in each treatment arm, at each visit. In general, the proportion of patients with concordant satisfactory microbiological and clinical outcomes was at least 90% for both treatment groups at both assessments. The proportion of patients with concordant unsatisfactory microbiological and clinical outcomes was at least 80.0% at the end-of-treatment visit and 100.0% at the post-treatment follow-up visit. There were no clinically relevant differences in concordance between treatment groups or between times of assessment.

The proportions of patients who were switched to oral antibiotic therapy were similar between treatment groups in the ITT, MITT, CE, and FE analysis sets. Three hundred twenty-five (31%) patients in the ITT analysis set took concomitant antibacterial medications, 163 (32%) patients randomized to meropenem and 162 (31%) patients randomized to imipenem-cilastatin. These patients included those who failed therapy for their primary

infection and those who required concomitant antibiotic for a concomitant infection. The most common concomitant antibacterial medication administered to at least 5% of patients in either treatment group was vancomycin. One thousand nineteen (98%) patients took concomitant non-antibacterial drugs, 500 (98%) patients randomized to meropenem and 519 (99%) patients randomized to imipenem-cilastatin. The most common concomitant non-antibacterial medications administered by at least 20% of patients in either treatment group were paracetamol (acetaminophen), morphine, regular insulin, and combination therapy of hydrocodone plus paracetamol. There were no clinically relevant differences in concomitant medications between treatment groups.

There were no statistically significant differences between treatment groups in time to hospital discharge for patients in the CE analysis set with satisfactory (unsatisfactory) clinical outcomes; 7.3 (13.2) days for patients randomized to meropenem versus 7.1 (12.2) days for patients randomized to imipenem-cilastatin.

Safety results

Overall, meropenem (500 mg iv every 8 hours) was well tolerated, and this study did not identify any issues for its use in hospitalized patients with complicated skin and skin structure infections.

The number of patients who had serious adverse events (SAEs) was similar between the meropenem and imipenem-cilastatin groups (Table S3). The number of patients who discontinued study treatment due to an AE (DAEs) was similar across the treatment groups. The number of patients who discontinued study treatment due to a SAE was approximately 1-2 % for each treatment group. The number of patients who died was also similar in the meropenem group (10 patients, 2%) compared to the imipenem-cilastatin group (9 patients, 1.7%).

Table S3 Number (%) of subjects who had at least 1 adverse event in any category, and total numbers of adverse events (safety population)

	Number (%) of patients who had an adverse event in each category[a]			
	Meropenem (N=511)		Imipenem-cilastatin (N=526)	
Category of adverse event	**n**	**(%)**	**n**	**(%)**
Any adverse events	297	(58.1)	298	(56.7)
Drug related	46	(9.0)	57	(10.8)
Leading to withdrawal	13	(2.5)	14	(2.7)
Deaths	10	(2.0)	9	(1.7)
Serious adverse events	41	(8.0)	43	(8.2)
Leading to death or immediately life-threatening	14	(2.7)	10	(1.9)
Not leading to death and not life threatening	31	(6.1)	37	(7.0)
Leading to withdrawal	9	(1.8)	6	(1.1)
Drug-related	3	(0.6)	2	(0.4)

Table S3 Number (%) of subjects who had at least 1 adverse event in any category, and total numbers of adverse events (safety population)

	Number (%) of patients who had an adverse event in each category[a]	
	Meropenem (N=511)	**Imipenem-cilastatin (N=526)**
Other significant adverse event	0	0
	Total number of adverse events	
Any adverse events	920	848
Drug-related adverse event	60	96
Serious adverse events-not leading to death and not life threatening	46	44
Drug-related serious adverse events	3	2

[a] Patients with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

The most commonly reported AEs (>5% in any group) were headache, nausea, constipation, diarrhea, anemia, pain, and pruritus for either treatment groups. Nausea, constipation and pruritus were reported by a larger proportion of patients in the imipenem-cilastatin group than in the meropenem group (Table S4).

The frequency of AEs was similar across the treatment groups, and the majority of AEs were assessed as mild to moderate in intensity by each investigator. In both treatment groups, less than 11% of the AEs were drug-related as assessed by the investigator; diarrhea was assessed to be drug-related in >2% of patients in both groups. In general across the treatment groups, the majority of the AEs occurred during the iv treatment phase. A similar trend was observed in either treatment groups for drug-related AEs.

There were no consistent patterns in AE incidence by age, gender, race or renal impairment across the treatment groups. The majority of the patients did not require renal dose adjustment for either treatment groups (927 of 1037 patients). Almost twice as many patients in the imipenem-cilastatin group (74 patients) required renal dose adjustment at the beginning of the study compared to the meropenem group (46 patients). This is because dose adjustment is required at a higher creatinine clearance for patients treated with imipenem-cilastatin.

Table S4 **Number (%) of subjects with the most commonly reported (≥5% in any treatment group) adverse events, sorted by decreasing order of frequency groups (safety population)**

	Meropenem (N=511)		Imipenem-cilastatin (N=526)	
COSTART Preferred term	**n**	**(%)**	**n**	**(%)**
Headache	40	(7.8)	33	(6.3)
Nausea	40	(7.8)	57	(10.8)
Constipation	36	(7.1)	44	(8.4)
Diarrhea	36	(7.0)	32	(6.1)
Anemia	28	(5.5)	21	(4.0)
Pain	26	(5.1)	20	(3.8)
Pruritus	25	(4.9)	31	(5.9)

[a]Common adverse events: Adverse events occurring at an incidence of ≥5% in any treatment group.
Patients with multiple events in the same category are counted only once in that category.
Patients with multiple events in more than one category are counted once in each of those categories.

The overall information from the laboratory results did not raise any safety concern for the use of meropenem for the treatment of hospitalized patients with complicated skin and skin structure infections.

Date of the report

28 May 2004