Supplementary Online Content

Brunkhorst FM, Oppert M, Marx G, et al; for the German Study Group Competence Network Sepsis (SepNet). Effect of empirical treatment with moxifloxacin and meropenem vs meropenem on sepsis-related organ dysfunction in patients with severe sepsis: a randomized trial. *JAMA*. doi:10.1001/jama.2012.5833

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Definitions of clinical and microbiological outcomes and protocol violations

Definitions of Clinical and Microbiological Outcomes

Clinical Cure (CC) and Microbiological Cure (MC) visits were performed at End Of Therapy (EOT) and End Of Study (EOS).

Clinical Cure
Clinical resolution: disappearance of acute signs and symptoms related to the infection or sufficient improvement such that additional or alternative antimicrobial therapy was not required.
Improvement: disappearance of acute signs and symptoms related to the infection or reduction in the severity and/or number of signs and symptoms of infection.
Clinical failure: failure to respond or insufficient improvement of the signs and symptoms of infection such that additional antimicrobial therapy was required.

Microbiological Cure
Documented microbiological eradication: the elimination of the putative pathogen from repeated culture of the site of infection.
Presumed microbiological eradication: disappearance of acute signs and symptoms related to the infection and no culture results available.
Documented microbiological persistence: Persistence of the enrollment microorganism from secretions of the site of infection throughout the study period.
Presumed microbiological persistence: clinical failure and no culture results from the site of infection available.
Relapse: after initial eradication, the patient had a clinical deterioration with the same organism that was responsible for the initial infection.
Superinfection: similar to relapse but involved a different or new organism.
Colonization: the acquisition (after enrollment) of yeast or bacteria not associated with features of infection.
Indeterminate: If a patient could not categorized according to one of the forementioned definitions.

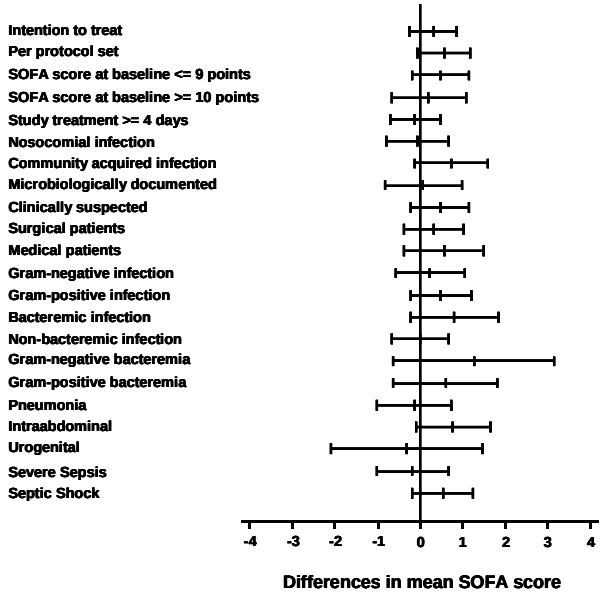
Response to therapy
Response to therapy visits were performed on study days 7 and 10.
Positive response to therapy: resolution of acute signs and symptoms related to the infection or reduction in the severity and/or number of signs and symptoms of infection (incl. decrease of procalcitonin plasma levels ≤1.0 ng/ml or decrease by ≥50% from day 4 to day 7, or from day 7 to day 10, respectively). In patients with pneumonia the clinical pulmonary infection score (CPIS) must be ≤1.0 points.
Negative response to therapy: no resolution of acute signs and symptoms related to the infection or no reduction in the severity and/or number of signs and symptoms of infection (incl. procalcitonin plasma levels > 1.0 ng/ml or no decrease by ≥50% from day 4 to day 7, or from day 7 to day 10, respectively). In patients with pneumonia the clinical pulmonary infection score (CPIS) is > 1.0 points.

Definitions of Protocol Violations
1. Violation of one or more inclusion or exclusion criteria
2. Non protocol-compatible administration of the study drugs:
    a. Study treatment (Meropenem and Moxifloxacin) administered > 6 hours after enrollment
    b. Moxifloxacin administered > 12 hours after enrollment
    c. The recommended daily dose of meropenem or moxifloxacin not administered for one complete study day
    d. Moxifloxacin administered in the monotherapy group
3. No additional antimicrobial therapy administered in case of:
    a. Bacteremia due to methicillin-resistant staphylococcei
    b. Bacteremia due enterococcei
    c. Bacteremia due to Candida spp.

4. Any additional antimicrobial therapy administered within the first 96 hours after enrollment (with the exception of 3 a-c).

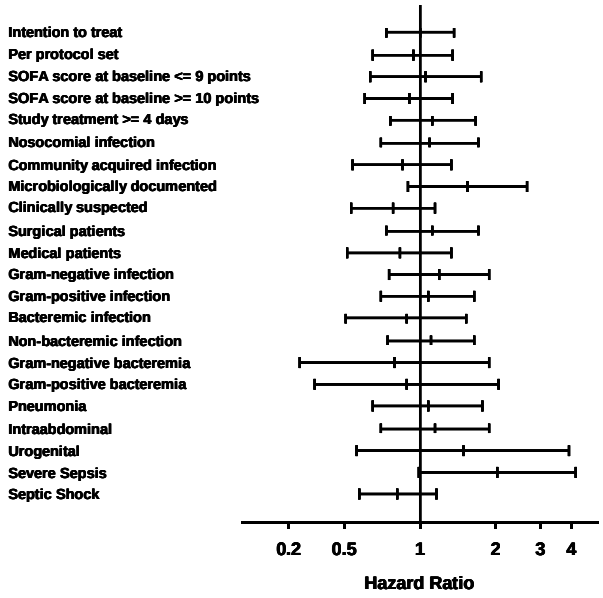
eFigure. Treatment effect of combination therapy on clinical outcome within various subgroups

A



	Monotherapy		Combination Therapy			
	No.	unadjusted meanSOFA and 95% CI	No.	unadjusted meanSOFA and 95% CI	adjusted difference and 95% CI	p-value
Intention to treat	252	7.9 (7.5; 8.4)	256	8.3 (7.8; 8.8)	0.3 (-0.2; 0.9)	0.275
Per protocol set	181	7.6 (7.0; 8.1)	198	7.9 (7.3; 8.5)	0.6 (-0.1; 1.2)	0.073
SOFA score at baseline <= 9 points	129	6.3 (5.8; 6.9)	141	6.9 (6.3; 7.5)	0.5 (-0.2; 1.2)	0.157
SOFA score at baseline >= 10 points	123	9.6 (8.9;10.3)	115	10.0 (9.1;10.8)	0.2 (-0.7; 1.1)	0.651
Study treatment >= 4 days	198	7.9 (7.4; 8.4)	200	7.8 (7.3; 8.3)	-0.1 (-0.7; 0.5)	0.688
Nosocomial infection	127	8.3 (7.7; 9.0)	126	8.2 (7.5; 8.9)	-0.1 (-0.8; 0.7)	0.864
Community acquired infection	125	7.6 (6.9; 8.3)	130	8.3 (7.5; 9.1)	0.7 (-0.1; 1.6)	0.090
Microbiologically documented	91	7.7 (6.9; 8.6)	90	8.0 (7.2; 8.7)	0.1 (-0.8; 1.0)	0.875
Clinically suspected	161	8.1 (7.5; 8.7)	166	8.5 (7.8; 9.1)	0.5 (-0.2; 1.2)	0.190
Surgical patients	135	7.8 (7.1; 8.4)	157	7.9 (7.3; 8.6)	0.3 (-0.4; 1.0)	0.363
Medical patients	117	8.2 (7.4; 8.9)	99	8.8 (7.9; 9.7)	0.6 (-0.4; 1.5)	0.245
Gram-negative infection	140	8.0 (7.3; 8.6)	109	8.8 (8.0; 9.5)	0.2 (-0.6; 1.0)	0.568
Gram-positive infection	130	7.9 (7.3; 8.6)	146	8.3 (7.6; 9.0)	0.5 (-0.2; 1.2)	0.183
Bacteremic infection	84	8.6 (7.7; 9.5)	85	9.3 (8.3;10.4)	0.8 (-0.2; 1.8)	0.126
Non-bacteremic infection	168	7.6 (7.0; 8.2)	171	7.8 (7.2; 8.3)	0.0 (-0.7; 0.7)	0.980
Gram-negative bacteremia	37	8.3 (7.0; 9.6)	28	10.9 (9.3;12.5)	1.3 (-0.6; 3.2)	0.185
Gram-positive bacteremia	46	8.0 (6.9; 9.1)	55	8.2 (6.9; 9.4)	0.6 (-0.6; 1.8)	0.335
Pneumonia	97	8.2 (7.5; 9.0)	111	8.4 (7.6; 9.2)	-0.1 (-1.0; 0.7)	0.766
Intraabdominal	92	7.8 (6.9; 8.6)	100	8.1 (7.3; 8.9)	0.8 (-0.1; 1.7)	0.086
Urogenital	36	8.2 (6.8; 9.6)	25	8.2 (6.8; 9.6)	-0.3 (-2.1; 1.5)	0.718
Severe Sepsis	65	7.2 (6.2; 8.1)	76	7.4 (6.5; 8.3)	-0.2 (-1.0; 0.7)	0.683
Septic Shock	187	8.2 (7.7; 8.8)	180	8.7 (8.0; 9.3)	0.5 (-0.2; 1.2)	0.145

B



	Monotherapy		Combination Therapy			
	No.	Death Cases	No.	Death Cases	adjusted HR (95% CI)	p-value
Intention to treat	273	85	276	96	1.00 (0.73; 1.36)	0.986
Per protocol set	199	59	214	70	0.94 (0.65; 1.35)	0.720
SOFA score at baseline <= 9 points	141	37	153	43	1.05 (0.63; 1.74)	0.864
SOFA score at baseline >= 10 points	132	48	123	53	0.90 (0.60; 1.34)	0.604
Study treatment >= 4 days	206	57	209	61	1.12 (0.76; 1.66)	0.572
Nosocomial infection	137	43	135	46	1.09 (0.70; 1.69)	0.710
Community acquired infection	136	42	141	50	0.84 (0.54; 1.32)	0.456
Microbiologically documented	97	32	98	28	1.54 (0.89; 2.66)	0.125
Clinically suspected	176	53	178	68	0.78 (0.53; 1.15)	0.209
Surgical patients	146	47	162	50	1.11 (0.73; 1.71)	0.618
Medical patients	127	38	114	46	0.82 (0.51; 1.32)	0.425
Gram-negative infection	149	47	120	46	1.19 (0.75; 1.88)	0.464
Gram-positive infection	140	43	155	53	1.07 (0.69; 1.64)	0.767
Bacteremic infection	90	30	93	37	0.88 (0.51; 1.52)	0.639
Non-bacteremic infection	183	55	183	59	1.10 (0.74; 1.63)	0.652
Gram-negative bacteremia	40	12	33	19	0.79 (0.33; 1.89)	0.597
Gram-positive bacteremia	49	14	58	15	0.88 (0.38; 2.06)	0.774
Pneumonia	105	32	119	38	1.07 (0.64; 1.77)	0.799
Intraabdominal	99	37	110	40	1.15 (0.70; 1.88)	0.591
Urogenital	39	14	25	8	1.48 (0.56; 3.92)	0.434
Severe Sepsis	74	18	84	20	2.01 (0.98; 4.12)	0.055
Septic Shock	199	67	192	76	0.81 (0.57; 1.16)	0.245

Adjusted generalized linear models for the effect of combination therapy on mean SOFA scores (Panel A) and adjusted proportional hazard models for the effect of addition of moxifloxacin on overall survival (Panel B).

Negative differences in mean SOFA and hazard ratios less than 1 represent a reduction of the mean SOFA score and the overall mortality, respectively, in favor of the combination therapy. No statistically significant association of the study treatment with clinical endpoints was observed for any of these subgroups of patients.

Models were adjusted for pre-treatment with antibiotics; age, SOFA score and renal failure at enrolment; bacterial resistance and gram-negative enrollment pathogens.

eTable 1. Antibiotics used one week prior to randomization*

	All n = 551	Monotherapy n = 273	Combination Therapy N = 278	p-value*
Penicillins	200 (36%)	93 (34%)	107 (38%)	0.28
Cephalosporins	175 (32%)	78 (29%)	97 (35%)	0.11
Other beta lactams	121 (22%)	59 (22%)	62 (22%)	0.85
Aminoglycosides	4 (1%)	2 (1%)	2 (1%)	1.00
Chinolones	38 (7%)	19 (7%)	19 (7%)	0.95
Glycopeptides	12 (2%)	5 (2%)	7 (3%)	0.77
Macrolides	23 (4%)	13 (5%)	10 (4%)	0.49
Other antibiotics	159 (29%)	76 (28%)	83 (30%)	0.60
No antibiotics	123 (22%)	67 (25%)	56 (20%)	0.22

* Data are presented as absolute frequencies and percentages in brackets.
† P values calculated by Chi-square test or Fisher's exact test, as appropriate.

eTable 2. Susceptibility patterns and numbers of resistant enrollment organisms*

	All n = 551	Monotherapy n = 273	Combination Therapy N = 278	p-value†
Meropenem §				
Citrobacter species	5 / 5 (100%)	5 / 5 (100%)	0 / 0	-
Enterobacter species	19 / 20 (95%)	10/11 (91%)	9 / 9 (100%)	1.00
Escherichia coli	78 / 78 (100%)	40 / 40 (100%)	38 / 38 (100%)	-
Klebsiella species	24 / 24 (100%)	14 / 14 (100%)	10 / 10 (100%)	-
Proteus species	14 / 14 (100%)	10 / 10 (100%)	4 / 4 (100%)	-
Pseudomonas aeruginosa	21 / 25 (84%)	10 / 13 (77%)	11 / 12 (92%)	0.59
Other pseudomonas species	1 / 3 (33%)	0 / 2 (0%)	1 / 1 (100%)	0.33
Bacteroides species	1 / 1 (100%)	1 / 1 (100%)	0 / 0	-
Resistant pathogens	4 / 127 (3%)	4 / 69 (6%)	0 / 58 (0%)	0.13
Moxifloxacin §				
Citrobacter species	5 / 5 (100%)	5 / 5 (100%)	0 / 0	-
Enterobacter species	12 / 12 (100%)	6 / 6 (100%)	6 / 6 (100%)	-
Escherichia coli	41 / 48 (85%)	20 / 23 (87%)	21 / 25 (84%)	1.00
Klebsiella species	11 / 14 (79%)	6 / 8 (75%)	5 / 6 (83%)	1.00
Proteus species	5 / 7 (71%)	4 / 6 (67%)	1 / 1(100%)	1.00
Pseudomonas aeruginosa	5 / 15 (33%)	2 / 10 (20%)	3 / 5 (60%)	0.25
Other pseudomonas species	1 / 3 (33%)	1 / 2 (50%)	0 / 1 (0%)	1.00
Bacteroides species	0 / 0	0 / 0	0 / 0	-
Resistant pathogens	17 / 74 (23%)	12 /42 (29%)	5 / 32 (16%)	0.27
Tobramycin or Gentamicin §				
Citrobacter species	5 / 5 (100%)	5 / 5 (100%)	0 / 0	-
Enterobacter species	19 / 21 (90%)	10 / 12 (83%)	9 / 9 (100%)	0.49
Escherichia coli	76 / 80 (95%)	37 / 40 (93%)	39 / 40 (98%)	0.62
Klebsiella species	25 / 26 (96%)	14 / 15 (93%)	11 / 11 (100%)	1.00
Proteus species	15 / 16 (94%)	10 / 10 (100%)	5 / 6 (83%)	0.38
Pseudomonas aeruginosa	23 / 25 (92%)	11 / 13 (85%)	12 / 12 (100%)	0.48
Other pseudomonas species	3 / 4 (75%)	2 / 3 (67%)	1 / 1 (100%)	1.00
Bacteroides species	1 / 1 (100%)	1 / 1 (100%)	0 / 0	-
Resistant pathogens	9 / 130 (7%)	7 / 70 (10%)	2 / 60 (3%)	0.18

* Data are presented as absolute frequencies and percentages in brackets. Analyses restricted to patients whose specimens were tested for susceptibility. The denominator is the subset of enrollment organisms tested for susceptibility against the named antibiotic.
† P values calculated by Fisher's exact test.
§ Multiple responses per patient possible

eTable 3. Adverse events*

	All n = 596	**Monotherapy n = 293**	**Combination Therapy n = 303**	**p-value†**
Patients with at least one				
Adverse Event (AE)	156 (26.2%)	71 (24.2%)	85 (28.1%)	0.31
	[22.7; 29.9]	[19.4; 29.6]	[23.1; 33.5]	
related	37 (6.2%)	11 (3.8%)	26 (8.6%)	0.02
	[4.4; 8.5]	[1.9; 6.6]	[5.7; 12.3]	
serious	32 (5.4%)	15 (5.1%)	17 (5.6%)	0.86
	[3.7; 7.5]	[2.9; 8.3]	[3.3; 8.8]	
serious related	10 (1.7%)	3 (1.0)	7 (2.3)	0.34
	[0.8; 3.1]	[0.2; 3.0]	[0.9; 4.7]	
AE resulting in death	45 (7.6%)	20 (6.8%)	25 (8.3%)	0.54
	[5.6; 10.0]	[4.2; 10.4]	[5.4; 11.9]	
related AE resulting in death	2 (0.3%)	0	2 (0.7%)	0.50
	[0.04; 1.2]	-	[0.1; 2.4]	

* Data are presented as absolute frequencies, percentages in brackets and 95 percent confidence intervals. Analysis based on Safety Analysis Population (see Method section).
† P Values calculated by Fisher's exact test.

eTable 4. Response to therapy, clinical and microbiological cure

	All n = 551	**Monotherapy n = 273**	**Combination Therapy n = 278**	**p-value***
Response to therapy day 7 †. – no. (%), 95% CI	112 / 311 (36.0) [30.7; 41.6]	57 / 151 (37.8) [30.0; 46.0]	55 / 160 (34.4) [27.1; 42.3]	0.49
Response to therapy day 10 †. – no. (%), 95% CI	56 / 134 (41.8) [33.3; 50.6]	25 / 64 (39.1) [27.1; 52.1]	31 / 70 (44.3) [32.4; 56.7]	0.48
Clinical Cure at EOT ‡ – no. (%), 95% CI				0.48
Clinical resolution	37 / 406 (9.1) [6.5; 12.3]	15 / 203 (7.4) [4.2; 11.9]	22 / 203 (10.8) [6.9; 16.0]	
Improvement	158 /406 (38.9) [34.2; 43.9]	81 / 203 (39.9) [33.1; 47.0]	77 / 203 (37.9) [31.2; 45.0]	
Clinical failure	211 / 406 (52.0) [47.0; 56.9]	107 / 203 (52.7) [45.6; 59.7]	104 / 203 (51.2) [44.1; 58.3]	
Missing	72	35	37	
Clinical Cure at EOS ‡– no. (%), 95% CI				0.19
Clinical resolution	49 / 374 (13.1) [9.9; 17.0]	19 / 190 (10.0) [6.1; 15.2]	30 / 184 (16.3) [11.3; 22.5]	
Improvement	140 / 374 (37.4) [32.5; 42.6]	75 / 190 (39.5) [32.5; 46.8]	65 / 184 (35.3) [28.4; 42.7]	
Clinical failure	185 /374 (49.5) [44.3; 54.7]	96 / 190 (50.5) [43.2; 57.8]	89 / 184 (48.4) [41.0; 55.8]	
Missing	66	34	32	
Microbiological Cure at EOT ‡ – no. (%), 95% CI				0.79
Documented microbiological eradication	143 / 404 (35.4) [30.7; 40.3]	66 / 203 (32.5) [26.1; 39.4]	77 / 201 (38.3) [31.6; 45.4]	
Presumed microbiological eradication	23 / 404 (5.7) [3.6; 8.4]	11 / 203 (5.4) [2.7; 9.5]	12 / 201 (6.0) [3.1; 10.2]	
Documented microbiological persistence	40 / 404 (9.9) [7.2; 13.2]	21 / 203 (10.3) [6.5; 15.4]	19 / 201 (9.5) [5.8; 14.4]	
Presumed microbiological persistence	82 / 404 (20.3) [16.5; 24.6]	44 / 203 (21.7) [16.2; 28.0]	38 / 201 (18.9) [13.7; 25.0]	
Superinfection	25 / 404 (6.2) [4.0; 9.0]	15 / 203 (7.4) [4.2; 11.9]	10 / 201 (5.0) [2.4; 9.0]	
Colonization	1 / 404 (0.3) [0.0; 1.4]	1 / 203 (0.5) [0.0; 2.7]	0	
Indeterminate	90 / 404 (22.3) [18.3; 26.7]	45 / 203 (22.2) [16.7; 28.5]	45 / 201 (22.4) [16.8; 28.8]	
Missing	74	35	39	
Microbiological Cure at EOS ‡– no. (%), 95% CI				0.73
Documented microbiological eradication	123 / 373 (33.0) [28.2; 38.0]	58 / 193 (30.1) [23.7; 37.1]	65 / 180 (36.1) [29.1; 43.6]	
Presumed microbiological eradication	35 / 373 (9.4) [6.6; 12.8]	16 / 193 (8.3) [4.8; 13.1]	19 / 180 (10.6) [6.5; 16.0]	
Documented microbiological persistence	23 / 373 (6.2) [4.0; 9.1]	14 / 193 (7.3) [4.0; 11.9]	9 / 180 (5.0) [2.3; 9.3]	

	All n = 551	Monotherapy n = 273	Combination Therapy n = 278	p-value*
Presumed microbiological persistence	77 / 373 (20.6) [16.7; 25.1]	42 / 193 (21.8) [16.2; 28.3]	35 / 180 (19.4) [13.9; 26.0]	
Superinfection	34 / 373 (9.1) [6.4; 12.5]	17 / 193 (8.8) [5.2; 13.7]	17 / 180 (9.4) [5.6; 14.7]	
Colonization	0	0	0	
Relapse	6 / 373 (1.6) [0.6; 3.5]	4 / 193 (2.1) [0.6; 5.2]	2 / 180 (1.1) [0.1; 4.0]	
Indeterminate	75 / 373 (20.1) [16.2; 24.5]	42 / 193 (21.8) [16.2; 28.3]	33 / 180 (18.3) [13.0; 24.8]	
Missing	67	31	36	

* P Values based on patient with valid information and calculated by Chi-square test or Fisher's exact test, as appropriate.
† Analyses restricted to patients who were still under study treatment on day 7 or day 10, respectively.
‡ Patients who withdrew informed consent or died before EOT or EOS, respectively, were excluded.
EOT = End of therapy
EOS = End of study

eTable 5. Protocol violations*

	All n = 551	**Monotherapy n = 273**	**Combination Therapy N = 278**
Patients with at least one protocol violation	136 (25%)	74 (27%)	62 (22%)
1. Violation of one or more inclusion or exclusion criteria	12 (2%)	6 (2%)	6 (2%)
2. Non protocol-compatible administration of the study drugs			
Study treatment administered > 6 hours after enrollment	19 (3%)	16 (6%)	3 (1%)
Moxifloxacin administered > 12 hours after enrollment	4 (1%)	0	4 (1%)
The recommended daily dose of meropenem not administered for one complete study day	8 (1%)	4 (1%)	4 (1%)
The recommended daily dose of moxifloxacin not administered for one complete study day	17 (3%)	0	17 (6%)
Moxifloxacin administered in the monotherapy group	5 (1%)	5 (2%)	0
3. No additional antimicrobial therapy administered in case of			
a) Bacteremia due to methicillin-resistant staphylococcei	3 (1%)	1 (<1%)	2 (1%)
b) Bacteremia due enterococcei	8 (1%)	5 (2%)	3 (1%)
c) Bacteremia due to Candida spp.	6 (1%)	2 (1%)	4 (1%)
4. Any additional antimicrobial therapy administered within the first 96 hours after enrolment (with the exception of 3 a-c)	77 (14%)	44 (16%)	33 (12%)

* Data are presented as absolute frequencies and percentages in brackets.