ELECTRONIC SUPPLEMENTARY MATERIAL

Real-world use, effectiveness, and safety of intravenous fosfomycin: the FORTRESS study

Klaus-Friedrich Bodmann[1,*], Stefan Hagel[2,*], Alessandra Oliva[3], Stefan Kluge[4], Alessandra Mularoni[5], Valentina Galfo[6], Marco Falcone[6], Mathias W. Pletz[2], Simone Lindau[7], Nadja Käding[8], Jan T. Kielstein[9], Michael Zoller[10], Carlo Tascini[11], Sebastian Kintrup[12], Dirk Schädler[13], Claudia Spies[14], Francesco Giuseppe De Rosa[15], Szilvia Radnoti[1], Alessandra Bandera[16], Roberto Luzzati[17], Sam Allen[18], Loredana Sarmati[19], Antonio Cascio[20], Nikolaos Kapravelos[21], Chinari Pradeep Kumar Subudhi[22], George Dimopoulos[23], Matthias G. Vossen[24], Abhijit M. Bal[25], Mario Venditti[3], Claudio Maria Mastroianni[3], Thomas Borrmann[26,#], Christian Mayer[26,#]

[*] Contributed equally

[#] Shared senior authorship

Affiliations:

[1] Kliniken Nordoberpfalz AG, Klinikum Weiden, Weiden, Germany

[2] Institute for Infectious Diseases and Infection Control, Jena University Hospital, Friedrich-Schiller-University, Jena, Germany

[3] Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome, Italy

[4] Department of Intensive Care Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[5] IRCCS-ISMETT, Palermo, Italy

[6] Department of Clinical and Experimental Medicine, Azienda Ospedaliero Universitaria Pisana, University of Pisa, Pisa, Italy

[7] Department of Anaesthesiology, Intensive Care Medicine and Pain Medicine, University Hospital Frankfurt, Goethe-University Frankfurt, Frankfurt, Germany

[8] Department of Infectious Diseases and Microbiology, University of Luebeck, Luebeck, Germany

[9] Medical Clinic V Nephrology, Rheumatology, Blood Purification - Academic Teaching Hospital Braunschweig, Braunschweig, Germany

[10] Department of Anaesthesiology, LMU University Hospital, LMU Munich, Munich, Germany

[11] Infectious Diseases Clinic, Department of Medicine (DMED), University of Udine, Udine, Italy

[12] University Hospital Muenster, Department of Anaesthesiology, Intensive Care and Pain Medicine, Muenster, Germany

[13] Department for Anaesthesiology and Intensive Care Medicine, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany

[14] Department of Anaesthesiology and Operative Intensive Care Medicine (CCM, CVK), Charité – Universitätsmedizin Berlin, Berlin, Germany

[15] Department of Medical Sciences, Infectious Diseases, University of Turin, Turin, Italy

[16] Infectious Diseases Unit, IRCCS Ca' Granda Ospedale Maggiore Policlinico Foundation, Milan, Italy

[17] Clinical Department of Medical, Surgical and Health Sciences, Trieste University, Trieste, Italy

[18] Department of Microbiology, University Hospital Crosshouse, Kilmarnock, United Kingdom

[19] Department of Infectious Diseases, University Hospital Tor Vergata, Rome, Italy

[20] Infectious and Tropical Diseases Unit, AOU Policlinico "P. Giaccone", University of Palermo, Palermo, Italy

[21] Intensive Care Unit, G Papanikolaou General Hospital, Exohi, Thessaloniki, Greece.

[22] Royal Bolton Hospital, Bolton, United Kingdom

[23] Third Department of Critical Care Medicine, National and Kapodistrian University of Athens, Medical School, Athens, Greece

[24] Division of Infectious Diseases and Tropical Medicine, Department of Internal Medicine I, Medical University of Vienna, Vienna, Austria

[25] Department of Microbiology, Queen Elizabeth University Hospital, Glasgow, United Kingdom

[26] InfectoPharm Arzneimittel und Consilium GmbH, Heppenheim, Germany

✉ **Corresponding author:**

Stefan Hagel, MD, MS

Institute for Infectious Diseases and Infection Control, Jena University Hospital, Friedrich-Schiller-University, Jena, Germany

Email: stefan.hagel@uni-jena.de

Table S1: Extended baseline characteristics

Characteristic*	716 patients *n* (%)
Concomitant treatment *(any)*	582 (81.3)
Diuretics	268 (37.4)
Initial fluid resuscitation	193 (27.0)
Vasopressors	201 (28.1)
Corticosteroids	182 (25.4)
Insulin	179 (25.0)
NSAIDs	161 (22.5)
Immunosuppressant	128 (17.9)
Inotropic therapy	61 (8.5)
Anticancer chemotherapy	20 (2.8)
Co-morbidities *(any)*	693 (96.8)
Cardiovascular	476 (66.5)
Congestive heart failure	*115 (24.2)*
Coronary heart disease	*136 (28.6)*
Hypertension	*354 (74.4)*
Other	*197 (41.4)*
Renal	253 (35.3)
Insufficiency	*196 (77.5)*
Renal replacement therapy	*55 (21.7)*
Other	*55 (21.7)*
Endocrinologic	252 (35.2)
Diabetes mellitus	*197 (78.2)*
Other	*68 (27.0)*
Electrolyte disorders	226 (31.6)
Hypernatraemia	*56 (24.8)*
Hyponatraemia	*71 (31.4)*
Hyperkalaemia	*26 (11.5)*
Hypokalaemia	*120 (53.1)*
Other	*11 (4.9)*
Respiratory	210 (29.3)
Pulmonary oedema	*11 (5.2)*
COPD	*85 (40.5)*
Bronchiectasis	*5 (2.4)*
Oncologic	128 (17.9)
Immunosuppressive	120 (16.8)
HIV	*3 (2.5)*
Post solid organ/bone marrow transplantation	*76 (63.3)*
Post chemotherapy/radiotherapy	*26 (21.7)*
Other	*18 (15.0)*
Hepatic	109 (15.2)
Cirrhosis	*33 (30.3)*
Other	*85 (78.0)*
Orthopaedic	100 (14.0)
Osteoporosis/-arthritis	*31 (31.0)*
Orthopaedic device	*37 (37.0)*
Other	*38 (38.0)*
Traumatic injury/fractures	60 (8.4)
Fracture	*54 (90.0)*
Other	*13 (21.7)*
Other	273 (38.1)
Tobacco use	140 (19.6)
Alcohol abuse	52 (7.3)
Drug abuse	24 (3.4)

* multiple entries possible; *COPD* chronic obstructive pulmonary disease*; HIV* human immunodeficiency virus*; NSAID* non-steroidal anti-inflammatory drug; *n* number of patients; percentages and numbers in italics are relative to the total number of patients in that category; immunocompromised was defined as patients receiving immunosuppressive/anticancer chemotherapy and/or patients with an immunosuppressive co-morbidity

Table S2: Demographics, baseline, and therapy characteristics of patients presenting with IE

Demography/characteristic*	46 patients
Age (years)	
Mean (SD)	61.8 (17.4)
Median	66.0
95% CI (mean)	[56.62; 66.94]
Range	19-87
Gender, *n* (%)	
Female	13 (28.3)
Male	33 (71.7)
Patients on ICU, *n (%)*	39 (84.8)
APACHE II score, *mean (SD) (n=9)*	22.1 (8.1)
SOFA score, *mean (SD) (n=4)*	8.0 (6.4)
Sepsis, *n (%)*	19 (41.3)
Septic shock, *n (%)*	3 (6.5)
Mechanical ventilation, *n (%)*	9 (19.6)
Creatinine clearance (ml/min), *mean (SD) (n=39)*	63.5 (35.3)
Co-morbidities *(any)***, *n (%)*	44 (95.7)
Cardiovascular	41 (89.1)
Congestive heart failure	*14 (34.1)*
Coronary heart disease	*12 (29.3)*
Hypertension	*28 (68.3)*
Other	*25 (61.0)*
Renal	25 (54.3)
Insufficiency	*23 (92.0)*
Renal replacement therapy	*4 (16.0)*
Other	*3 (12.0)*
Electrolyte disorder	15 (32.6)
Hypernatraemia	*2 (13.3)*
Hyponatraemia	*7 (46.7)*
Hyperkalaemia	*1 (6.7)*
Hypokalaemia	*9 (60.0)*
Targeted therapy, *n (%)*	31 (67.4)
Line of treatment, *n (%)*	
Patients treated in 1st line	1 (2.2)
Patients treated in 2nd line	31 (67.4)
Patients treated in 3rd line	14 (30.4)
Echocardiography, *n (%)*	39 (88.6)
Associated surgery, *n (%)*	19 (41.3)
Infection details, *n (%)*	
Left-sided	33 (71.7)
Right-sided	5 (10.9)
Both-sided	8 (17.4)
Acute infection	45 (97.8)
Subacute infection	1 (2.2)
Prosthetic valve	30 (65.2)
Cardiac electronic device	7 (15.2)
Vegetation	36 (78.3)
Abscess	8 (17.4)
Embolic complications, *n (%)*	6 (13.0)
Stroke	*3 (50.0)*
Splenic infarction	*1 (16.7)*
Other	*2 (33.3)*
Haemorrhages, *n (%)*	1 (2.2)

* multiple entries possible; ** patients may have also had other co-morbidities not listed; *APACHE II* acute physiology and chronic health evaluation II; *CI* confidence interval; *ICU* intensive care unit; *IE* infective endocarditis; *SD* standard deviation; *SOFA* sepsis-related organ failure assessment score; *n* number of patients; percentages and numbers in italics are relative to the total number of patients in that category

Table S3: Demographics and baseline characteristics of patients with *S. aureus* bacteraemia

Demography/characteristic*	125 patients
Age *(years)*	
Mean *(SD)*	62.1 (14.0)
Median	62.0
95% CI *(mean)*	[59.64; 64.55]
Range	19-85
Gender, *n (%)*	
Female	34 (27)
Male	91 (73)
Patients on ICU, *n (%)*	66 (52.8)
APACHE II score, *mean (n*=11)	18.9
SOFA score, *mean (n*=10)	4.0
Sepsis, *n (%)*	54 (43.2)
Septic shock, *n (%)*	9 (7.2)
Mechanical ventilation, *n (%)*	16 (12.8)
Creatinine clearance (ml/min), *median (range) (n=39)*	73 (5-385)
Co-morbidities*, n (%)*	
Cardiovascular	101 (80.8)
Congestive heart failure	*33 (32.7)*
Coronary heart disease	*37 (36.6)*
Hypertension	*73 (72.3)*
Other	*47 (46.5)*
Renal	40 (32.0)
Insufficiency	*37 (92.5)*
Renal replacement therapy	*6 (15.0)*
Other	*3 (7.5)*
Electrolyte disorder	38 (30.4)
Hypernatraemia	*3 (7.9)*
Hyponatraemia	*16 (42.1)*
Hyperkalaemia	*8 (21.1)*
Hypokalaemia	*18 (47.4)*
Targeted therapy, *n (%)*	95 (76.0)
Source of infection, *n (%)*	
Pneumonia	8 (6.4)
Urinary tract infection	3 (2.4)
Skin/soft tissue infection	18 (14.4)
Intraabdominal infection	2 (1.6)
Vertebral osteomyelitis	23 (18.4)
Endocarditis	32 (25.6)
Meningitis	2 (1.6)
Catheter-associated infection	6 (4.8)
Device-associated infection	4 (3.2)
Unknown	13 (10.4)
Other	26 (20.8)
MRSA bacteraemia, *n (%)*	22 (20.8)
Low-risk MRSA bacteraemia	*11 (50.0)*
High-risk MRSA bacteraemia	*11 (50.0)*
MSSA bacteraemia, *n (%)*	105 (84.0)
Low-risk MSSA bacteraemia	*64 (61.0)*
High-risk MSSA bacteraemia	*41 (39.0)*
Low-risk *S. aureus* bacteraemia (MSSA and MRSA), *n (%)*	74 (59.2)
High-risk *S. aureus* bacteraemia (MSSA and MRSA), *n (%)*	51 (40.8)

* multiple entries possible; *APACHE II* acute physiology and chronic health evaluation II; *CI* confidence interval; *ICU* intensive care unit; MRSA methicillin-resistant *S. aureus;* MSSA methicillin-susceptible *S. aureus*; *SD* standard deviation; *SOFA* sepsis-related organ failure assessment score; *n* number of patients; percentages and numbers in italics are relative to the total number of patients in that category

Table S4: Indications of IV fosfomycin use, stratified by country

Indication/country	*n (%)*
Austria (*n*=16)	
BJI	6 (37.5)
Spondylodiscitis	*4 (66.7)*
Diabetic foot osteomyelitis	*2 (33.3)*
cSSTI	3 (18.8)
HAP/VAP	1 (6.3)
IE	1 (6.3)
Bacteraemia/sepsis	1 (6.3)
other	4 (25.0)
Germany (*n*=427)	
Bacteraemia/sepsis	80 (18.7)
BJI	78 (18.3)
Spondylodiscitis	*42 (53.8)*
PJI	*16 (20.5)*
Diabetic foot	*3 (3.8)*
Long bone osteomyelitis	*3 (3.8)*
Osteomyelitis - other	*14 (17.9)*
BM/CNSI	54 (12.6)
cSSTI	52 (12.2)
IE	44 (10.3)
cUTI	42 (9.8)
HAP/VAP	40 (9.4)
Other	37 (8.7)
Greece (*n*=16)	
HAP/VAP	11 (68.8)
Bacteraemia/sepsis	2 (12.5)
cUTI	2 (12.5)
BM/CNSI	1 (6.3)
Italy (*n*=236)	
Bacteraemia sepsis	82 (34.7)
cUTI	74 (31.4)
BJI	38 (16.1)
PJI	*8 (21.1)*
Spondylodiscitis	*7 (18.4)*
Long bone osteomyelitis	*6 (15.8)*
Diabetic foot osteomyelitis	*2 (5.3)*
Osteomyelitis - other	*15 (39.5)*
HAP/VAP	23 (9.8)
cSSTI	10 (4.2)
IE	1 (0.4)
BM/CNSI	1 (0.4)
Other	7 (3.0)
UK (*n*=21)	
cUTI	11 (52.4)
Bacteraemia/sepsis	4 (19.0)
HAP/VAP	4 (19.0)
BJI	2 (9.5)
Long bone osteomyelitis	*1 (50.0)*
PJI	*1 (50.0)*

BJI bone and joint infection; *BM/CNSI* bacterial meningitis/CNS (central nervous system) infection; *CoNS* coagulase-negative staphylococci; *cSSTI* complicated skin and soft tissue infection; *cUTI* complicated urinary tract infection; *HAP/VAP* hospital-acquired/ventilator-associated pneumonia; *IE* infective endocarditis; *MRSA* methicillin-resistant *S. aureus*; *MSSA* methicillin-sensitive *S. aureus*; *PJI* periprosthetic joint infection; *spp.* species; *UK* United Kingdom; *n* number of patients; percentages and numbers in italics are relative to the total number of patients in that category

Table S5: Isolated pathogens per indication, stratified by country

Country/indication	MSSA, *n* (%)	MRSA, *n* (%)	*Klebsiella* spp., *n* (%)	*Enterobacter* spp., *n* (%)	CoNS, *n* (%)	*P. aeruginosa*, *n* (%)	*Enterococcus* spp., *n* (%)	*E. coli*, *n* (%)	*Proteus* spp., *n* (%)	*Streptococcus* spp., *n* (%)	Other, *n* (%)
Austria (*n*=7)											
Bacteraemia/sepsis (*n*=1)	1 (100)	-	-	-	-	-	-	-	-	-	-
IE (*n*=1)	1 (100)	-	-	-	-	-	-	-	-	-	-
cSSTI (*n*=1)	1 (100)	-	-	-	-	-	-	-	-	-	-
HAP/VAP (*n*=1)	-	-	1 (100)	-	-	-	-	-	-	-	-
Other infections (*n*=3)	1 (33.3)	-	-	-	-	-	-	1 (33.3)	-	1 (33.3)	-
Germany (*n*=538)											
Bacteraemia/sepsis (*n*=123)	43 (35.0)	12 (9.8)	5 (4.1)	5 (4.1)	14 (11.4)	6 (4.9)	8 (6.5)	13 (10.6)	4 (3.3)	3 (2.4)	10 (8.1)
BJI (*n*=95)											
Spondylodiscitis (*n*=39)	23 (59.0)	4 (10.3)	-	-	5 (12.8)	-	1 (2.6)	1 (2.6)	-	4 (10.3)	1 (2.6)
PJI (*n*=25)	7 (28.0)	2 (8.0)	2 (8.0)	-	5 (20.0)	1 (4.0)	3 (12.0)	3 (12.0)	-	1 (4.0)	1 (4.0)
Long bone osteomyelitis (*n*=8)	2 (25.0)	-	1 (12.5)	-	1 (12.5)	-	1 (12.5)	1 (12.5)	-	-	2 (25.0)
Diabetic foot osteomyelitis (*n*=6)	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	-	-	-	-	-
Osteomyelitis – other (*n*=17)	6 (35.3)	2 (11.8)	1 (5.9)	1 (5.9)	2 (11.8)	-	1 (5.9)	4 (23.5)	-	-	-
cSSTI (*n*=74)	22 (29.7)	2 (2.7)	2 (2.7)	5 (6.8)	8 (10.8)	5 (6.8)	3 (4.1)	8 (10.8)	3 (4.1)	8 (10.8)	8 (10.8)
IE (*n*=51)	25 (49.0)	4 (7.8)	-	1 (2.0)	11 (21.6)	1 (2.0)	2 (3.9)	1 (2.0)	-	3 (5.9)	3 (5.9)
BM/CNSI (*n*=50)	6 (12.0)	-	3 (6.0)	5 (10.0)	20 (40.0)	1 (2.0)	1 (2.0)	4 (8.0)	1 (2.0)	3 (6.0)	6 (12.0)
HAP/VAP (*n*=47)	5 (10.6)	2 (4.3)	6 (12.8)	2 (4.3)	8 (17.0)	4 (8.5)	4 (8.5)	3 (6.4)	2 (4.3)	1 (2.1)	10 (21.3)
cUTI (*n*=44)	3 (6.8)	-	7 (15.9)	3 (6.8)	1 (2.3)	3 (6.8)	6 (13.6)	12 (27.3)	4 (9.1)	-	5 (11.4)
Other infections (*n*=54)	19 (35.2)	1 (1.9)	2 (3.7)	1 (1.9)	4 (7.4)	4 (7.4)	5 (9.3)	6 (11.1)	3 (5.6)	2 (3.7)	7 (13.0)
Greece (*n*=21)											
HAP/VAP (*n*=13)	-	-	6 (46.2)	-	-	2 (15.4)	1 (7.7)	-	1 (7.7)	-	3 (23.1)
Bacteraemia/sepsis (*n*=5)	-	-	2 (40.0)	-	1 (20.0)	1 (20.0)	-	-	-	-	1 (20.0)
cUTI (*n*=2)	-	-	2 (100)	-	-	-	-	-	-	-	-
BM/CNSI (*n*=1)	-	-	-	-	-	-	-	-	-	-	1 (100)

Table S5: continued

Country/indication	MSSA, *n* (%)	MRSA, *n* (%)	*Klebsiella* spp., *n* (%)	*Enterobacter* spp., *n* (%)	CoNS, *n* (%)	*P. aeruginosa*, *n* (%)	*Enterococcus* spp., *n* (%)	*E. coli*, *n* (%)	*Proteus* spp., *n* (%)	*Streptococcus* spp., *n* (%)	Other, *n* (%)
Italy (*n*=250)											
Bacteraemia/sepsis (*n*=88)	9 (10.2)	4 (4.5)	33 (37.5)	2 (2.3)	6 (6.8)	5 (5.7)	6 (6.8)	10 (11.4)	2 (2.3)	3 (3.4)	8 (9.1)
cUTI (*n*=78)	-	1 (1.3)	30 (38.5)	-	-	7 (9.0)	8 (10.3)	20 (25.6)	4 (5.1)	-	8 (10.3)
BJI (*n*=38)											
Spondylodiscitis (*n*=8)	5 (62.5)	-	-	1 (12.5)	-	-	-	2 (25.0)	-	-	-
PJI (*n*=7)	-	-	4 (57.1)	-	1 (14.3)	-	-		1 (14.3)	1 (14.3)	-
Long bone osteomyelitis (*n*=7)	3 (42.9)	-	1 (14.3)	-	-	1 (14.3)	-	2 (28.6)	-	-	-
Diabetic foot osteomyelitis (*n*=3)	-	-	-	1 (33.3)	-	1 (33.3)	-	-	1 (33.3)	-	-
Osteomyelitis – other (*n*=13)	4 (30.8)	-	-	1 (7.7)	-	4 (30.8)	-	2 (15.4)	-	1 (7.7)	1 (7.7)
HAP/VAP (*n*=19)	-	-	5 (26.3)	1 (5.3)	2 (10.5)	6 (31.6)	1 (5.3)	1 (5.3)	-	-	3 (15.8)
cSSTI (*n*=18)	3 (16.7)	1 (5.6)	2 (11.1)	-	1 (5.6)	6 (33.3)	3 (16.7)	-	-	1 (5.6)	1 (5.6)
BM/CNSI (*n*=1)	-	-	1 (100)	-	-	-	-	-	-	-	-
IE (*n*=1)	1 (100)	-	-	-	-	-	-	-	-	-	-
Other infections (*n*=7)	1 (14.3)	1 (14.3)	4 (57.1)	-	1 (14.3)	-	-	-	-	-	-
UK (*n*=21)											
cUTI (*n*=13)	-	-	2 (15.4)	-	-	-	-	7 (53.8)	-	-	4 (30.8)
Bacteraemia/sepsis (*n*=5)	-	-	-	-	1 (20.0)	-	2 (40.0)	1 (20.0)	-	-	1 (20.0)
HAP/VAP (*n*=1)	-	-	-	-	-	-	-	-	-	-	1 (100)
BJI (*n*=2)											
PJI (*n*=1)	-	-	-	-	-	-	-	-	-	-	1 (100)
Long bone osteomyelitis (*n*=1)	-	-	-	-	-	1 (100)	-	-	-	-	-

BJI bone and joint infection; *BM/CNSI* bacterial meningitis/CNS (central nervous system) infection; *CoNS* coagulase-negative staphylococci; *cSSTI* complicated skin and soft tissue infection; *cUTI* complicated urinary tract infection; *HAP/VAP* hospital-acquired/ventilator-associated pneumonia; *IE* infective endocarditis; *MRSA* methicillin-resistant *S. aureus*; *MSSA* methicillin-sensitive *S. aureus*; *PJI* periprosthetic joint infection; *spp.* species; *UK* United Kingdom; *n* number of documented isolates

Table S6: Extended summary of antibiotics used in combination with IV fosfomycin

Main antibiotic classes/antibiotics used in combination[*, #]	716 patients *n* (%)
Beta lactam/beta-lactamase inhibitor combination	181 (25.3)
Piperacillin/tazobactam	*93 (51.4)*
Ceftazidime/avibactam	*50 (27.6)*
Ampicillin/sulbactam	*22 (12.2)*
Meropenem/vaborbactam	*9 (5.0)*
Ceftolozane/tazobactam	*6 (3.3)*
Amoxicillin/clavulanic acid	*1 (0.6)*
Carbapenems	157 (21.9)
Meropenem	*146 (93.0)*
Imipenem/cilastatin	*9 (5.7)*
Ertapenem	*2 (1.3)*
Penicillins	109 (15.2)
Flucloxacillin	*91 (83.5)*
Oxacillin	*9 (8.3)*
Ampicillin	*4 (3.7)*
Benzylpenicillin	*4 (3.7)*
Sultamicillin	*1 (0.9)*
Glycopeptides	103 (14.4)
Vancomycin	*99 (96.1)*
Teicoplanin	*3 (2.9)*
Oritavancin	*1 (1.0)*
3rd/4th/5th/next generation cephalosporins	80 (11.2)
Ceftriaxone	*25 (31.3)*
Ceftazidime	*17 (21.3)*
Cefepime	*14 (17.5)*
Cefotaxime	*10 (12.5)*
Cefiderocol	*6 (7.5)*
Ceftaroline	*5 (6.3)*
Ceftobiprole	*3 (3.8)*
1st /2nd generation cephalosporins	79 (11.0)
Cefazolin	*69 (87.3)*
Cefuroxime	*10 (12.7)*
Lipopeptide antibiotics	56 (7.8)
Daptomycin	*56 (100)*
Fluoroquinolones	37 (5.2)
Ciprofloxacin	*25 (67.6)*
Levofloxacin	*12 (32.4)*
Aminoglycosides	28 (3.9)
Amikacin	*16 (57.1)*
Gentamicin	*11 (39.3)*
Tobramycin	*1 (3.6)*
Oxazolidinones	*23 (3.2)*
Linezolid	*23 (100)*
Polymyxins	16 (2.2)
Colistin	*16 (100)*
Lincosamides	12 (1.7)
Clindamycin	*12 (100)*
Macrolide	12 (1.7)
Clarithromycin	*8 (66.7)*
Erythromycin	*4 (33.3)*

Table S6: continued

Main antibiotic classes/antibiotics used in combination[*, #]	716 patients *n* (%)
Diaminopyrimidines/sulfonamides	10 (1.4)
Trimethoprim/sulfamethoxazole	*10 (100)*
Nitroimidazoles	9 (1.3)
Metronidazole	*9 (100)*
Rifamycins	9 (1.3)
Rifampicin	*7 (77.8)*
Rifaximin	*2 (22.2)*
Glycylcyclines	9 (1.3)
Tigecycline	*9 (100)*
Monobactams	4 (0.6)
Aztreonam	*4 (100)*

[*] multiple entries possible; [#] start of combination partner max. 1 day after FOS start; *n* number of patients; percentages and numbers in italics are relative to the total number of patients in that category

Table S7: Clinical and microbiological outcomes by indication, subgroups, main pathogens, and most frequently used combination partners at IR

	Cases, *n*	Clinical success, *n* (%)	Clinical response, *n* (%)	Clinical failure, *n* (%)	Microbiological cure, *n* (%)
All patients*	716	420 (58.7)	504 (70.4)	14 (2.0)	500 (69.8)
Indication*					
Bacteraemia/sepsis#	169	100 (59.2)	118 (69.8)	8 (4.7)	123 (72.8)
Treated with daily dose > 16 g+	26	19 (73.1)	19 (73.1)	0 (0)	20 (76.9)
Treated with daily dose ≤ 16 g+	143	81 (56.6)	99 (69.2)	8 (5.6)	103 (72.0)
cUTI	129	103 (79.8)	111 (86.0)	0 (0)	110 (85.3)
Treated with daily dose > 16 g+	15	13 (86.7)	13 (86.7)	0 (0)	13 (86.7)
Treated with daily dose ≤ 16 g+	114	90 (78.9)	98 (86.0)	0 (0)	97 (85.1)
Patients treated in monotherapy	47	41 (87.2)	43 (91.5)	0 (0)	43 (91.5)
BJI	124	66 (53.2)	81 (65.3)	2 (1.6)	83 (66.9)
Treated with daily dose > 16 g+	18	10 (55.6)	11 (61.1)	0 (0)	11 (61.1)
Treated with daily dose ≤ 16 g+	106	56 (52.8)	70 (66.0)	2 (1.9)	72 (67.9)
Spondylodiscitis	53	26 (49.1)	31 (58.5)	0 (0)	38 (71.7)
PJI	25	15 (60.0)	19 (76.0)	2 (8.0)	16 (64.0)
Long bone osteomyelitis	10	5 (50.0)	6 (60.0)	0 (0)	5 (50.0)
Diabetic foot	7	2 (28.6)	4 (57.1)	0 (0)	2 (28.6)
Osteomyelitis – other	29	18 (62.1)	21 (72.4)	0 (0)	22 (75.9)
HAP/VAP	79	37 (46.8)	50 (63.3)	3 (3.8)	44 (55.7)
Treated with daily dose > 16 g+	24	10 (41.7)	13 (54.2)	1 (4.2)	14 (58.3)
Treated with daily dose ≤ 16 g+	55	27 (49.1)	37 (67.3)	2 (3.6)	30 (54.5)
cSSTI	65	28 (43.1)	39 (60.0)	1 (1.5)	31 (47.7)
Treated with daily dose > 16 g+	16	7 (43.8)	9 (56.3)	0 (0)	7 (43.8)
Treated with daily dose ≤ 16 g+	49	21 (42.9)	30 (61.2)	1 (2.0)	24 (49.0)
BM/CNSI	56	35 (62.5)	43 (76.8)	0 (0)	42 (75.0)
Treated with daily dose > 16 g+	32	20 (62.5)	25 (78.1)	0 (0)	24 (75.0)
Treated with daily dose ≤ 16 g+	24	15 (62.5)	18 (75.0)	0 (0)	18 (75.0)
Infective endocarditis	46	23 (50.0)	26 (56.5)	0 (0)	34 (73.9)
Foreign body involvement	35	17 (48.6)	20 (57.1)	0 (0)	26 (74.3)
W/o foreign body involvement	11	6 (54.5)	6 (54.5)	0 (0)	8 (72.7)
With abscess involvement	8	3 (37.5)	5 (62.5)	0 (0)	5 (62.5)
Concomitant sepsis/septic shock	21	10 (47.6)	13 (61.9)	0 (0)	13 (61.9)
Treated with daily dose > 16 g+	10	6 (60.0)	7 (70.0)	0 (0)	8 (80.0)
Treated with daily dose ≤ 16 g+	36	17 (47.2)	19 (52.8)	0 (0)	26 (72.2)
Other	48	28 (58.3)	36 (75.0)	0 (0)	33 (68.8)
Treated with daily dose > 16 g+	6	5 (83.3)	5 (83.3)	0 (0)	5 (83.3)
Treated with daily dose ≤ 16 g+	42	23 (54.8)	31 (73.8)	0 (0)	28 (66.7)

Table S7: continued

	Cases, *n*	Clinical success, *n* (%)	Clinical response, *n* (%)	Clinical failure, *n* (%)	Microbiological cure, *n* (%)
Subpopulation[*]					
All patients with sepsis/septic shock at baseline	298	156 (52.3)	198 (66.4)	9 (3.0)	192 (64.4)
Immunocompromised patients	163	108 (66.3)	123 (75.5)	4 (2.5)	123 (75.5)
Non-immunocompromised patients	553	312 (56.4)	381 (68.9)	10 (1.8)	377 (68.2)
Patients treated with daily dose > 16 g[+]	147	90 (61.2)	102 (69.4)	1 (0.7)	102 (69.4)
Patients treated with daily dose ≤ 16 g[+]	569	330 (58.0)	402 (70.7)	13 (2.3)	398 (69.9)
Pathogens[$, §, *]					
E. coli	99	60 (60.6)	69 (69.7)	3 (3.0)	69 (69.7)
Enterobacter spp.	30	19 (63.3)	23 (76.6)	0 (0)	20 (66.7)
Klebsiella spp.	119	81 (68.1)	98 (82.4)	0 (0)	86 (72.3)
Proteus spp.	26	18 (69.2)	21 (80.8)	0 (0)	19 (73.1)
P. aeruginosa	58	31 (53.4)	41 (70.7)	0 (0)	35 (60.3)
MRSA	37	22 (59.5)	25 (67.6)	0 (0)	29 (78.4)
MSSA	189	98 (51.9)	125 (66.1)	3 (1.6)	128 (67.7)
CoNS	88	55 (62.5)	62 (70.5)	3 (3.4)	66 (75.0)
Enterococcus spp.	54	30 (55.6)	38 (70.4)	3 (5.6)	34 (63.0)
GP pathogens[1]	269	154 (57.2)	188 (69.9)	6 (2.2)	199 (74.0)
GN pathogens[2]	238	157 (66.0)	184 (77.3)	3 (1.3)	175 (73.5)
GP plus GN infections (polybacterial)	86	45 (52.3)	54 (62.8)	2 (2.3)	51 (59.3)
CR pathogens	77	51 (66.2)	60 (77.9)	0 (0)	54 (70.1)
MDR pathogens	241	158 (65.6)	180 (74.7)	6 (2.5)	183 (75.9)
Combination partners[§, *]					
Meropenem	146	78 (53.4)	98 (67.1)	4 (2.7)	91 (62.3)
Vancomycin	99	55 (55.6)	70 (70.7)	1 (1.0)	66 (66.7)
Flucloxacillin	91	47 (51.6)	62 (68.1)	1 (1.1)	62 (68.1)
Piperacillin/tazobactam	93	55 (59.1)	68 (73.1)	3 (3.2)	62 (66.7)
Cefazolin	69	33 (47.8)	39 (56.5)	0 (0)	46 (66.7)
Daptomycin	56	31 (55.4)	35 (62.5)	1 (1.8)	40 (71.4)
Ceftazidime/avibactam	50	33 (66.0)	39 (78.0)	0 (0)	35 (70.0)

[*] ± bacteraemia and/or sepsis/septic shock; [#] clinically suspected or microbiologically ensured; [§] multiple entries possible; [$] without involvement of fungi, viruses, or other non-bacterial microorganisms; [+] initial targeted daily dose; [1] patients presenting with infections caused solely by GP pathogens; [2] patients presenting with infections caused solely by GN pathogens; *BJI* bone and joint infection; *BM/CNSI* bacterial meningitis/CNS (central nervous system) infection; *CoNS* coagulase-negative staphylococci; *CR* carbapenem-resistant; *cSSTI* complicated skin and soft tissue infection; *cUTI* complicated urinary tract infection; *GN* gram-negative; *GP* gram-positive; *HAP/VAP* hospital-acquired/ventilator-associated pneumonia; *IE* infective endocarditis; *MDR* multi-drug resistant; *MRSA* methicillin-resistant *S. aureus*; *MSSA* methicillin-sensitive *S. aureus*; *PJI* periprosthetic joint infection; *spp.* species; *IR* initial response; *w/o* without; *n* number of patients;

Table S8: Clinical and microbiological outcomes by indication, subgroups, main pathogens, and most frequently used combination partners at TOC

	Cases, *n*	Clinical success, *n* (%)	Clinical response, *n* (%)	Clinical failure, *n* (%)	Microbiological cure, *n* (%)
All patients[*]	716	560 (78.2)	614 (85.8)	51 (7.1)	601 (83.9)
Indication[*]					
Bacteraemia/sepsis[#]	169	127 (75.1)	141 (83.4)	16 (9.5)	140 (82.8)
Treated with daily dose > 16 g[+]	26	22 (84.6)	23 (88.5)	2 (7.7)	22 (84.6)
Treated with daily dose ≤ 16 g[+]	143	105 (73.4)	118 (82.5)	14 (9.8)	118 (82.5)
cUTI	129	111 (86.0)	116 (89.9)	3 (2.3)	117 (90.7)
Treated with daily dose > 16 g[+]	15	11 (73.3)	13 (86.7)	0 (0)	11 (73.3)
Treated with daily dose ≤ 16 g[+]	114	100 (87.7)	103 (90.4)	3 (2.6)	106 (93.0)
Patients treated in monotherapy	47	41 (87.2)	43 (91.5)	2 (4.3)	43 (91.5)
BJI[**]	124	94 (75.8)	105 (84.7)	10 (8.1)	102 (82.3)
Treated with daily dose > 16 g[+]	18	15 (83.3)	15 (83.3)	0 (0)	15 (83.3)
Treated with daily dose ≤ 16 g[+]	106	79 (74.5)	90 (84.9)	10 (9.4)	87 (82.1)
Long bone osteomyelitis[**]	10	8 (80.0)	9 (90.0)	1 (10.0)	8 (80.0)
Spondylodiscitis[**]	53	34 (64.2)	40 (75.5)	6 (11.3)	39 (73.6)
PJI[**]	25	21 (84.0)	22 (88.0)	3 (12.0)	23 (92.0)
Diabetic foot osteomyelitis[**]	7	4 (57.1)	5 (71.4)	0 (0)	5 (71.4)
Osteomyelitis – other[**]	29	27 (93.1)	29 (100.0)	0 (0)	27 (93.1)
HAP/VAP	79	52 (65.8)	61 (77.2)	8 (10.1)	53 (67.1)
Treated with daily dose > 16 g[+]	24	17 (70.8)	19 (79.2)	1 (4.2)	17 (70.8)
Treated with daily dose ≤ 16 g[+]	55	35 (63.6)	42 (76.4)	7 (12.7)	36 (65.5)
cSSTI	65	50 (76.9)	57 (87.7)	4 (6.2)	54 (83.1)
Treated with daily dose > 16 g[+]	16	14 (87.5)	15 (93.8)	0 (0)	15 (93.8)
Treated with daily dose ≤ 16 g[+]	49	36 (73.5)	42 (85.7)	4 (8.2)	39 (79.6)
BM/CNSI	56	48 (85.7)	52 (92.9)	3 (5.4)	50 (89.3)
Treated with daily dose > 16 g[+]	32	29 (90.6)	30 (93.8)	1 (3.1)	30 (93.8)
Treated with daily dose ≤ 16 g[+]	24	19 (79.2)	22 (91.7)	2 (8.3)	20 (83.3)
IE	46	37 (80.4)	37 (80.4)	5 (10.9)	42 (91.3)
Foreign body involvement	35	28 (80.0)	28 (80.0)	5 (14.3)	32 (91.4)
W/o foreign body involvement	11	9 (81.8)	9 (81.8)	0 (0)	10 (90.9)
With abscess involvement	8	7 (87.5)	7 (87.5)	0 (0)	8 (100)
Concomitant sepsis/septic shock	21	16 (76.2)	16 (76.2)	3 (14.3)	18 (85.7)
Treated with daily dose > 16 g[+]	10	10 (100)	10 (100)	0 (0)	10 (100)
Treated with daily dose ≤ 16 g[+]	36	27 (75.0)	27 (75.0)	5 (13.9)	32 (88.9)
Other infections[*]	48	41 (85.4)	45 (93.8)	2 (4.2)	43 (89.6)
Treated with daily dose > 16 g[+]	6	5 (83.3)	5 (83.3)	1 (16.7)	6 (100)
Treated with daily dose ≤ 16 g[+]	42	36 (85.7)	40 (95.2)	1 (2.4)	37 (88.1)

Table S8: continued

	Cases, *n*	Clinical success, *n* (%)	Clinical response, *n* (%)	Clinical failure, *n* (%)	Microbiological cure, *n* (%)
Subpopulation[*]					
All patients with sepsis/septic shock at baseline	298	217 (72.8)	237 (79.5)	35 (11.7)	238 (79.9)
Immunocompromised patients	163	134 (82.2)	145 (89.0)	12 (7.4)	141 (86.5)
Non-immunocompromised patients	553	426 (77.0)	469 (84.8)	39 (7.1)	460 (83.2)
Patients treated with daily dose > 16 g[+]	147	123 (83.7)	130 (88.4)	5 (3.4)	126 (85.7)
Patients treated with daily dose ≤ 16 g[+]	569	437 (76.8)	484 (85.1)	46 (8.1)	475 (83.5)
Pathogens[$, §, *]					
E. coli	99	79 (79.8)	88 (88.9)	4 (4.0)	83 (83.8)
Enterobacter spp.	30	24 (80.0)	26 (86.7)	2 (6.7)	25 (83.3)
Klebsiella spp.	119	101 (84.9)	110 (92.4)	2 (1.7)	104 (87.4)
Proteus spp.	26	22 (84.6)	25 (96.2)	0 (0)	22 (84.6)
P. aeruginosa	58	46 (79.3)	53 (91.4)	2 (3.4)	48 (82.8)
MRSA	37	27 (73.0)	30 (81.1)	4 (10.8)	32 (86.5)
MSSA	189	148 (78.3)	157 (83.1)	19 (10.1)	164 (86.8)
CoNS	88	70 (79.5)	76 (86.4)	7 (8.0)	76 (86.4)
Enterococcus spp.	54	42 (77.8)	48 (88.9)	3 (5.6)	45 (83.3)
GP pathogens[1]	269	214 (79.6)	229 (85.1)	26 (9.7)	236 (87.7)
GN pathogens[2]	238	199 (83.6)	214 (89.9)	12 (5.0)	206 (86.6)
GP plus GN infections (polybacterial)	86	67 (77.9)	75 (87.2)	4 (4.7)	73 (84.9)
CR pathogens	77	63 (81.8)	67 (87.0)	3 (3.9)	65 (84.4)
MDR pathogens	241	195 (80.9)	209 (86.7)	16 (6.6)	210 (87.1)
Combination partners[§, *]					
Meropenem	146	111 (76.0)	125 (85.6)	11 (7.5)	113 (77.4)
Vancomycin	99	75 (75.8)	85 (85.9)	11 (11.1)	79 (79.8)
Flucloxacillin	91	68 (74.7)	72 (79.1)	11 (12.1)	78 (85.7)
Piperacillin/tazobactam	93	71 (76.3)	82 (88.2)	3 (3.2)	76 (81.7)
Cefazolin	69	52 (75.4)	56 (81.2)	6 (8.7)	58 (84.1)
Daptomycin	56	42 (75.0)	43 (76.8)	10 (17.9)	49 (87.5)
Ceftazidime/avibactam	50	45 (90.0)	47 (94.0)	0 (0)	46 (92.0)

[*] ± bacteraemia and/or sepsis/septic shock; [**] (where available) clinical response at follow-up in BJI patients: 69/80 (86.3%), in spondylodiscitis patients: 24/36 (66.7%), in PJI patients: 12/14 (85.7%), in patients with long bone osteomyelitis: 4/5 (80.0%), in patients with diabetic foot osteomyelitis: 4/5 (80.0%), in patients with other osteomyelitis-related infections: 15/20 (75.0%); [#] clinically suspected or microbiologically ensured; [§] multiple entries possible; [$] without involvement of fungi, viruses, or other non-bacterial microorganisms; [+] initial targeted daily dose; [1] patients presenting with infections caused solely by GP pathogens; [2] patients presenting with infections caused solely by GN pathogens; *BJI* bone and joint infection; *BM/CNSI* bacterial meningitis/CNS (central nervous system) infection; *CoNS* coagulase-negative staphylococci; *CR* carbapenem-resistant; *cSSTI* complicated skin and soft tissue infection; *cUTI* complicated urinary tract infection; *GN* gram-negative; *GP* gram-positive; *HAP/VAP* hospital-acquired/ventilator-associated pneumonia; IE infective endocarditis; *MDR* multi-drug resistant; *MSSA* methicillin-sensitive *S. aureus*; *MRSA* methicillin-resistant *S. aureus*; *PJI* periprosthetic joint infection; *spp.* species; *TOC* test-of-cure; *w/o* without; *n* number of patients

Table S9: Clinical and microbiological outcomes in patients with bacteraemia caused by *S. aureus* or CR pathogens at IR

	Cases, *n*	Clinical success, *n* (%)	Clinical response, *n* (%)	Clinical failure, *n* (%)	Microbiological cure, *n* (%)
Bacteraemia[$]					
S. aureus bacteraemia[*]	125	67 (53.6)	82 (65.6)	2 (1.6)	92 (73.6)
MRSA	22	13 (59.1)	14 (63.6)	0 (0)	17 (77.3)
MSSA	105	54 (51.4)	68 (64.8)	2 (1.9)	75 (71.4)
Due to CR pathogens[*]	22	19 (86.4)	20 (90.9)	0 (0)	19 (86.4)

[*] patients with allocation of the term "bacteraemia/sepsis" (due to *S. aureus* or CR pathogens) as the applicable kind of infection by the investigator at start of FOS treatment and/or positive blood culture for the respective pathogen in patients allocated to another indication (only monobacterial infections were included); [$] without involvement of fungi, viruses, or other non-bacterial microorganisms; *CR* carbapenem-resistant; *FOS* intravenous fosfomycin; *MRSA* methicillin-resistant *S. aureus*; *MSSA* methicillin-susceptible *S. aureus; IR* initial response; *n* number of patients

Table S10: Clinical and microbiological outcomes in patients with bacteraemia caused by *S. aureus* or CR pathogens at TOC

	Cases, *n*	Clinical success, *n* (%)	Clinical response, *n* (%)	Clinical failure, *n* (%)	Microbiological cure, *n* (%)
Bacteraemia[$]					
S. aureus bacteraemia[*]	125	93 (74.4)	100 (80.0)	15 (12.0)	108 (86.4)
MRSA	22	14 (63.6)	16 (72.7)	4 (18.2)	18 (81.8)
MSSA	105	79 (75.2)	84 (80.0)	11 (10.5)	90 (85.7)
Due to CR pathogens[*]	22	19 (86.4)	20 (90.9)	1 (4.5)	19 (86.4)

[*] patients with allocation of the term "bacteraemia/sepsis" (due to *S. aureus* or CR pathogens) as the applicable kind of infection by the investigator at start of FOS treatment and/or positive blood culture for the respective pathogen in patients allocated to another indication (only monobacterial infections were included); [$] without involvement of fungi, viruses, or other non-bacterial microorganisms; *CR* carbapenem-resistant; *FOS* intravenous fosfomycin; *MRSA* methicillin-resistant *S. aureus*; *MSSA* methicillin-susceptible *S. aureus; TOC* test-of-cure; *n* number of patients

Table S11: Overview of reported adverse drug reactions

Type/organ class[*, **]	*n* ADR (*n* SADR)	716 patients % ADR (% SADR)
Metabolism and nutrition disorders		
Hypokalaemia	144 (51)	20.1 (7.1)
Hypernatraemia	107 (2)	14.9 (0.3)
Hyperkalaemia	7 (0)	1.0 (0)
Hyponatraemia	4 (1)	0.6 (0.1)
Decreased appetite	1 (0)	0.1 (0)
Hypoalbuminaemia	1 (0)	0.1 (0)
Hypocalcaemia	1 (0)	0.1 (0)
Gastrointestinal disorders		
Nausea	7 (0)	1.0 (0)
Diarrhoea	3 (0)	0.4 (0)
Vomiting	3 (0)	0.4 (0)
Abdominal pain upper	1 (0)	0.1 (0)
General disorders and administration site conditions		
Drug ineffective	4 (2)	0.6 (0.3)
Oedema peripheral	2 (0)	0.3 (0)
Infection site thrombosis	1 (0)	0.1 (0)
Investigations		
GGT increased	2 (0)	0.3 (0)
Transaminases increased	2 (0)	0.3 (0)
ALT increased	1 (0)	0.1 (0)
Blood sodium increased	1 (0)	0.1 (0)
Culture urine positive	1 (0)	0.1 (0)
Cardiac disorders		
Sinus tachycardia	1 (0)	0.1 (0)
Ventricular tachycardia	0 (1)	0 (0.1)
Hepatobiliary disorders		
Acute hepatic failure	0 (1)	0 (0.1)
Cholelithiasis	1 (0)	0.1 (0)
Infections and infestations		
Pathogen resistance[#]	0 (2)	0 (0.3)
Skin and subcutaneous tissue disorders		
Erythema	1 (0)	0.1 (0)
Pruritus	1 (0)	0.1 (0)
Blood and lymphatic system disorders		
Leukopenia	1 (0)	0.1 (0)
Eye disorders		
Diplopia	1 (0)	0.1 (0)
Psychiatric disorders		
Hallucination	1 (0)	0.1 (0)
Respiratory, thoracic, and mediastinal disorders		
Dyspnoea	1 (0)	0.1 (0)

[*] multiple entries possible; [**] patients with multiple events of the same ADR/SADR are counted as 1, multiple listing of patients with non-serious ADR and SADR possible; [#] suspected development of resistance; *ADR* adverse drug reaction (non-serious); *ALT* alanine aminotransferase; *GGT* Gamma glutamyltransferase; *SADR* serious ADR; *n* number of patients

Table S12: Summary of measured sodium and potassium levels

Type of electrolyte imbalance	716 patients *n* (%)
Hypokalaemia*	189 (26.4)
Potassium value [mmol/l]	
< 2.5	*24 (12.7)*
2.5 – 2.9	*83 (43.9)*
3 – 3.5	*82 (43.4)*
Hypernatraemia*	109 (15.4)
Sodium value [mmol/l]	
> 160	*12 (11.0)*
156 – 160	*22 (20.2)*
151 – 155	*31 (28.4)*
145 - 150	*44 (40.4)*

* including both ADRs and SADRs (on patient-level); *ADR* adverse drug reaction; *SADR* serious ADR; *n* number of patients; percentages and numbers in italics are relative to the total number of patients in that category

Table S13: List of principal investigators, and Ethics Committees approvals*

Country	Centre ID	PI	Centre	Ethics committee address	Date of approval
Germany	1	Günther, Ulf	Klinikum Oldenburg AöR	Carl von Ossietzky Universität Oldenburg, Ethikkommission, Carl-von-Ossietzky-Str. 9-11, 26129 Oldenburg Reference No.: 161/2016	22/02/2017
Germany	2	Schädler, Dirk	Universitätsklinikum Schleswig-Holstein, Campus Kiel	Medizinische Fakultät der Christian-Albrechts-Universität Kiel, Ethikkommission, Arnold-Heller-Straße 3/Haus 9, 24105 Kiel Reference No.: B214/17	31/01/2017
Germany	3	Lindau, Simone	Universitätsklinikum Frankfurt	Ethikkommission des Fachbereichs Medizin, Universitätsklinikum der Goethe-Universität, Theodor-Stern-Kai 7, 60596 Frankfurt Reference No.: 504/16	10/02/2017
Germany	4	Kluge, Stefan	Universitätsklinikum Hamburg-Eppendorf	Ethikkommission der Ärztekammer Hamburg, Weidestraße 22b, 22083 Hamburg Reference No.: MC-363/16	15/12/2016
Germany	5	Pletz, Mathias W.	Universitätsklinikum Jena	Universitätsklinikum Jena, Ethikkommission, Bachstraße 18, 07743 Jena Reference No.: 5037-01/17	18/01/2017
Germany	6	Kieninger, Martin	Universitätsklinikum Regensburg	Universität Regensburg, Ethikkommission, Landshuter Straße 4, 93047 Regensburg Reference No.: 16-160-0263	25/01/2017
Germany	7	Spies, Claudia	Charité – Universitätsmedizin Berlin	Charité – Universitätsmedizin Berlin, Ethikkommission, Campus Mitte, Charitéplatz 1, 10117 Berlin Reference No.: AZ798/16	14/02/2017

Table S13: continued

Country	Centre ID	PI	Centre	Ethics committee address	Date of approval
Germany	8	Kindgen-Milles, Detlef	Universitätsklinikum Düsseldorf	Medizinische Fakultät Düsseldorf, Ethikkommission, Moorenstraße 5, 40225 Düsseldorf Reference No.: 5906R/2017034165	29/06/2017
Germany	9	Gerlach, Herwig	Vivantes Klinikum Neukölln	No approval by local Ethics Committee required for non-interventional studies	
Germany	10	Zoller, Michael	LMU Klinikum der Universität München	Ludwig-Maximilians-Universität München, Ethikkommission, Pettenkoferstraße 8, 80336 München Reference No.: 17-043	09/05/2017
Germany	11	Radnoti, Szilvia	Kliniken Nordoberpfalz AG, Klinikum Weiden	Ethikkommission der Bayerischen Landesärztekammer, Mühlbaurstraße 16, 81677 München Reference No.: mb BO17034	28/08/2017
Germany	13	Kielstein, Jan T.	Städtisches Klinikum Braunschweig gGmbH	No approval by local Ethics Committee required for non-interventional studies	
Germany	14	Rupp, Jan	Universitätsklinikum Schleswig-Holstein, Campus Lübeck	Universität zu Lübeck, Ethikkommission, Ratzeburger Allee 160, 23538 Lübeck Reference No.: 19-076	28/02/2019
Germany	15	Kintrup, Sebastian	Universitätsklinikum Münster	Ethikkommission der Ärztekammer Westfalen-Lippe und der Westfälischen Wilhelms-Universität, Gartenstraße 210-214, 48147 Münster Reference No.: 2020-201-b-S	25/03/2020
Germany	Bodmann, Klaus-Friedrich (International medical coordinator)			Central: Ethikkommission der Landesärztekammer Brandenburg, Dreifertstraße 12, 03044 Cottbus Reference No.: S 19(a)/2016	26/10/2016

Table S13: continued

Country	Centre ID	PI	Centre	Ethics committee address	Date of approval
Italy	100	Mastroianni, Claudio	Azienda Ospedaliero-Universitaria Policlinico Umberto I, Roma	Central: Azienda Ospedaliero-Universitaria, Policlinico Umberto I, Comitato etico, Viale del Policlinico 155, 00161 Roma Reference No.: 5063	28/11/2018
Italy	101	Petrosillo, Nicola	Istituto Nazionale per le Malattie Infettive "Lazzaro Spallanzani", IRCCS, Roma	Istituto Nationale per le Malattie Infettive LAZZARO SPALLANZANI Comitato Etico Via Portuense, 292 00149 Roma Reference No.: 129	21/03/2019
Italy	102	Del Bono, Valerio	Azienda Ospedaliera S.Croce e Carle, Cuneo	COMITATO ETICO INTERAZIENDALE A. O. “Santa Croce e Carle” di Cuneo AA.SS.LL. Cuneo 1, Cuneo 2, Asti. Via Monte Zovetto, 18 12100 Cuneo Reference No.: 19-2019	23/03/2017
Italy	103	Bandera, Alessandra	Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano	Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico: Direzione Scientifica Comitato Etico - Milano Area 2 Via Francesco Sforza, 28 20122 Milano Reference No.: 0028254	10/12/2019
Italy	104	Falcone, Marco	Azienda Ospedaliera Università Pisana	Comitato Etico Regionale per la Sperimentazione Clinica della Regione Toscana Sezione: AREA VASTA NORD OVEST Via Roma, 67 56126 Pisa Reference No.: 15710_Falcone	03/03/2020

Table S13: continued

Country	Centre ID	PI	Centre	Ethics committee address	Date of approval
Italy	105	Tascini, Carlo	Ospedale Santa Maria della Misericordia, Udine	Comitato Etico Unico Regionale c/o Direzione Scientifica del CRO - Centro di riferimento Oncologico di Aviano Istituto di ricovero e cura a carattere scientifico Via Franco Gallini 2 33081 Aviano (PN) Reference No.: 2652	10/03/2020
Italy	106	Mularoni, Alessandra	Istituto Mediterraneo per i Trapianti ISMETT IRCCS, Palermo	Al Comitato Etico Sezionale IRCCS ISMETT Via E. Tricomi, 5 90127 Palermo Reference No.: IRRB/42/18	19/07/2019
Italy	107	Antinori, Spinello Domenico	Ospedale Luigi Sacco, Milano	Spett.le Comitato Etico Milano Area 1 ASST Fatenbenefratelli SaccoVia G.B. Grassi 74 20157 Milano Reference No.: 2019/ST/101	10/10/2019
Italy	108	Grossi, Paolo Antonio	ASST - Sette Laghi, Varese	ASST dei Sette Laghi Comitato Etico Viale Borri, 57 21100 Varese Reference No.: 61983	16/11/2021
Italy	109	Sarmati, Loredana	Policlinico Tor Vergata, Roma	Comitato Etico Indipendente presse la Fondazione PTV Policlinico Tor Vergata, Viale Oxford, 81 00133 Roma Reference No.: 68.21	30/04/2021

Table S13: continued

Country	Centre ID	PI	Centre	Ethics committee address	Date of approval
Italy	110	De Rosa, Francesco Giuseppe	Ospedale Cardinal Massaia, Asti - Dipartimento di Scienze Mediche, Università di Torino	Comitato Etico Interaziendale A.O.U. Città della Salute e della Scienza di Torino Corso Bramante 88/90 10126 Torino Reference No.: 0109038	21/10/2021
Italy	111	Bassetti, Matteo	Ospedale Policlinico San Martino – IRCCS, Genoa	Comitato Etico Regionale Ospedale Policlinico San Martino – IRCCS Largo R. Benzi,10 16132 Genova Reference No.: 11458	14/03/2022
Italy	112	Saracino, Annalisa	Policlinico di Bari	Comitato Etico Interregionale Sede: Policlinico di Bari P.zza G. Cesare n. 11 Bari 70124 Reference No.: 7446	30/11/2022
Italy	113	Luzzati, Roberto	Ospedale Maggiore, Trieste	Comitato Etico Unico Regionale del Friuli-Venezia Giulia c/o ARCS - Azienda Regionale di Coordinamento per la Salute Sede legale: Via Pozzuolo, 330 33100 Udine Reference No.: 2652	24/05/2022
Italy	114	Cascio, Antonio	Policlinico Paolo Giaccone, Palermo	Comitato Etico Palermo 1 Via del Vespro 129 90127 Palermo Reference No.: 03/2022	15/03/2022
Italy	115	Gentile, Ivan	Azienda Ospedaliera Universitaria Federico II, Napoli	Comitato Etico Università Federico II A.O.R.N. Cardarelli Via S. Pansini, 5 80131 Napoli Reference No.: 06/22	12/07/2022

Table S13: continued

Country	Centre ID	PI	Centre	Ethics committee address	Date of approval
United Kingdom	200	Allen, Sam	University Hospital Crosshouse, Kilmarnock	Central: Scotland A Research Ethic Committee Research Ethics Service 2-4 Waterloo Place Edinburgh EH1 3EG REC reference: 18/SS/0130	30/11/2018
United Kingdom	201	Parcell, Benjamin J.	Ninewells Hospital, Dundee	Central: Scotland A Research Ethic Committee Research Ethics Service 2-4 Waterloo Place Edinburgh EH1 3EG REC reference: 18/SS/0130	30/11/2018
United Kingdom	202	Barlow, Gavin	Castle Hill Hospital, Cottingham	Central: North West Haydock Research Ethic Committee Barlow House, 4 Minshull Street Manchester M1 3DZ REC reference: 18/NW/0696	10/12/2018
United Kingdom	203	Subudhi, Chinari Pradeep Kumar	Royal Bolton Hospital	Central: North West Haydock Research Ethic Committee Barlow House, 4 Minshull Street Manchester M1 3DZ REC reference: 18/NW/0696	10/12/2018

Table S13: continued

Country	Centre ID	PI	Centre	Ethics committee address	Date of approval
United Kingdom	204	Moore, Luke S. P.	Chelsea and Westminster Hospital, London	Central: North West Haydock Research Ethic Committee Barlow House, 4 Minshull Street Manchester M1 3DZ REC reference: 18/NW/0696	10/12/2018
United Kingdom	205	Bal, Abhijit M.	Queen Elizabeth University Hospital, Glasgow	Central: Scotland A Research Ethic Committee Research Ethics Service 2-4 Waterloo Place Edinburgh EH1 3EG REC reference: 18/SS/0130	30/11/2018
United Kingdom	206	Satta, Giovanni	University College London Hospitals NHS Foundation Trust	Central: North West Haydock Research Ethic Committee Barlow House, 4 Minshull Street Manchester M1 3DZ REC reference: 18/NW/0696	10/12/2018
United Kingdom	207	Cepeda, Jorge	Lewisham and Greenwich NHS Trust, London	Central: North West Haydock Research Ethic Committee Barlow House, 4 Minshull Street Manchester M1 3DZ REC reference: 18/NW/0696	10/12/2018
United Kingdom	208	Murphy, Michael E.	NHS GGC Glasgow Royal Infirmary	Central: Scotland A Research Ethic Committee Research Ethics Service 2-4 Waterloo Place Edinburgh EH1 3EG REC reference: 18/SS/0130	30/11/2018

Table S13: continued

Country	Centre ID	PI	Centre	Ethics committee address	Date of approval
Austria	300	Vossen, Matthias G.	Allgemeines Krankenhaus Wien	Central: Ethikkommission der Medizinischen Universität Wien Borschkegasse 8b/6 1090 Wien Reference No.: 1333/2020	18/05/2020
Austria	301	Ladner, Eugen	Bezirkskrankenhaus Reutte	Central: Ethikkommission der Medizinischen Universität Wien Borschkegasse 8b/6 1090 Wien Reference No.: 1333/2020	18/05/2020
Austria	302	Gattringer, Rainer	Klinikum Wels-Grieskirchen GmbH	Central: Ethikkommission der Medizinischen Universität Wien Borschkegasse 8b/6 1090 Wien Reference No.: 1333/2020	18/05/2020
Austria	304	Graziadei, Ivo	Landeskrankenhaus Hall – Tirol Kliniken	Central: Ethikkommission der Medizinischen Universität Wien Borschkegasse 8b/6 1090 Wien Reference No.: 1333/2020	18/05/2020
Austria	305	Antonitsch, Lukas	Landesklinikum Wiener Neustadt	Central: Ethikkommission der Medizinischen Universität Wien Borschkegasse 8b/6 1090 Wien Reference No.: 1333/2020	18/05/2020

Table S13: continued

Country	Centre ID	PI	Centre	Ethics committee address	Date of approval
Greece	400	Avgeropoulou, Stavrina	Sotiria Thoracic Diseases Hospital, Athens	"SOTIRIA" Thoracic Diseases Hospital of Athens 152 Mesogion Avenue, 115 27, Athens Reference No.: 22826	16/09/2021
Greece	401	Kapravelos, Nikolaos	General Hospital G. Papanikolaou, Thessaloniki	General Hospital of Thessaloniki "G. Papanikolaou" Papanikolaou Avenue, Pilea – Chortiatis, 57010, Thessaloniki Reference No.: 4th regular meeting	19/04/2021
Greece	402	Mouloudi, Eleni	Hippokration General Hospital, Thessaloniki	General Hospital of Thessaloniki "Hippokration" 49, Konstantinoupoleos Avenue, Thessaloniki, 54623 Reference No.: 199	28/06/2021
Greece	403	Marangos, Markos N.	University General Hospital of Patras "Panagia Voithia"	University General Hospital of Patras "Panagia Voithia" Patras at Rio, 26504 Reference No.: 307	07/06/2021
Greece	404	Alamanos, Ioannis	General Hospital of Attica KAT, Athens	General Hospital of Attica KAT 2, Nikis St., 14561, Kifissia Reference No.: 16th meeting	17/09/2021

*All principal investigators/sites with Ethics Committee approval up to the data lock point (November 2023) are listed.