inoculation. *In vivo* antifungal activity was determined in a tail-vein IA model in neutropenic mice inoculated with *A. fumigatus* (AF) ATCC 204305 ($N = 10$ per dose). Two separate studies were conducted, with oral VT-1598 treatment starting either 48 hours prior (prophylaxis) or 5 hours postinoculation (delayed), with 4 days of postinoculation dosing, and kidney fungal burden measured 1 day post last dose by both CFU and qPCR. Drug control was 10 mg/kg AmBisome i.v.

Results. The MIC for VT-1598 against AF 204305 was 0.25 µg/mL. The plasma PK of VT-1598 was linearly proportional between the 5 and 40 mg/kg once-daily doses, with AUCs of 155 and 1,033 µg h/mL for the two doses, respectively. VT-1598 was similarly effective in reducing fungal burden when given in delayed treatment compared with prophylaxis, and both studies demonstrated a full dose–response (i.e., no to full reduction of fungal burden). When comparing fungal burdens of each dose group to the fungal burden at the start of treatment, the dose of VT-1598 to achieve fungal stasis ranged from 20.5 to 25.9 mg/kg and to achieve a 1-$\log_{10}$ fungal kill ranged from 30.9 to 50.5 mg/kg. Using the previously measured mouse plasma binding (>99.9%), the free AUC /MIC values for stasis and 1-$\log_{10}$ kill ranged from 2.1–2.7 and 3.2–5.2, respectively. These values are within the range of 1–11 that have been reported for posaconazole and isavuconazole (Lepak, AAC, 2013).

Conclusion. VT-1598 had potent antifungal activity in a murine model of IA. The PK/PD relationship was the same as clinically used mold-active CYP51 agents, suggesting that it could have similar clinical efficacy. If correct, the tetrazole-based greater selectivity may significantly differentiate VT-1598 from current IA therapies.

Disclosures. **E. P. Garvey**, Viamet Pharmaceuticals, Inc.: Employee, Salary. **A. Sharp**, Evotec (UK) Ltd.: Employee, Salary. **P. Warn**, Evotec (UK) Ltd.: Employee, Salary. **C. M. Yates**, Viamet Pharmaceuticals, Inc.: Employee, Salary. **R. J. Schotzinger**, Viamet Pharmaceuticals, Inc.: Board Member and Employee, Salary.

1347. Omadacycline for Acute Bacterial Skin and Skin Structure Infections: Integrated Analysis of Randomized Clinical Trials

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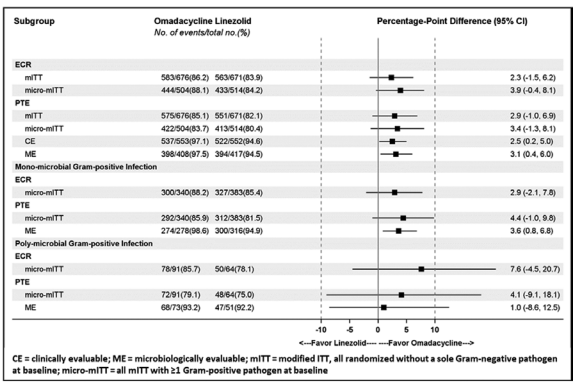
Background. Skin infections are a significant medical burden for affected individuals and the healthcare system. The purpose of this investigation was to integrate the findings of two randomized studies of omadacycline (OMC) in ABSSSI.

Methods. OMC in Acute Skin and Skin Structure Infections Study (OASIS)-1 initiated patients on intravenous (IV) OMC or linezolid (LZD) with a possible transition to oral formulation after at least 3 days of IV therapy. OASIS-2 investigated oral-only OMC. Treatment duration in both studies was 7–14 days. Early clinical response (ECR) in the mITT population, the primary endpoint in both studies, was defined as a ≥20% reduction in lesion size at 48–72 hours after treatment initiation. The secondary endpoint was investigator assessment of clinical response (IACR) at post-therapy evaluation (PTE) in the mITT and CE populations, 7–14 days after treatment initiation.

Results. A total of 691 patients receiving OMC and 689 patients receiving LZD were included. The mean age of patients was 45 years, 64% were male, and 83% enrolled at US sites. Infection types: wound infections (46.8%), cellulitis/erysipelas (30.5%), major abscess (22.7%). Median lesion size was 316 cm^2 and 304 cm^2 in OMC and LZD patients, respectively. *S. aureus* was detected in 74.6% of patients, of which 43.4% had MRSA. 71% were mono-microbial Gram-positive infections, 15% were poly-microbial Gram-positive infections. OMC showed similar efficacy to LZD for the primary and secondary endpoints, as well as for mono-microbial and poly-microbial infections (figure). Clinical responses were similar across different infection types, lesion sizes, and baseline pathogens. Treatment-emergent adverse events (TEAEs), most mild or moderate, were reported by 51% and 41% of patients receiving OMC or LZD, respectively. Nausea and vomiting were more frequent for OMC patients in the OASIS-2 oral-only study while receiving the loading dose on Day 1 and 2. Serious AEs were reported by 2.3% and 1.9%, respectively. TEAEs leading to study drug discontinuation were reported by 1.7% and 1.5%, respectively.

Conclusion. The integrated analysis of OASIS trials showed that oral and IV omadacycline was effective in the treatment of ABSSSI and was safe and generally well-tolerated by patients.



Disclosures. **F. M. Abrahamian**, Allergan: Speaker's Bureau, Speaker honorarium. Melinta: Speaker's Bureau, Speaker honorarium. Merck: Speaker's Bureau, Speaker honorarium. Nabriva: Scientific Advisor, Consulting fee. Paratek: Scientific Advisor, Consulting fee. **G. Sakoulas**, Allergan: Consultant and Speaker, Consulting fee and Speaker honorarium. Sunovion Pharmaceuticals: Speaker, Speaker honorarium. The Medicines Company: Speaker, Speaker honorarium. Paratek Pharmaceuticals: Consultant, Consulting fee. Cidara Therapeutics: Scientific Advisor, Consulting fee. Arsanis Pharmaceuticals: Scientific Advisor, Consulting fee. **E. Tzanis**, Paratek Pharmaceuticals: Employee, Salary. **A. Manley**, Paratek Pharmaceuticals: Employee and Shareholder, Salary. **J. N. Steenbergen**, Paratek Pharmaceuticals: Employee and Shareholder, Salary. **A. Das**, Achaogen: Consultant, Consulting fee. Cempra: Consultant, Consulting fee. Contrafect: Consultant, Consulting fee. Nabriva: Consultant, Consulting fee. Paratek: Consultant, Consulting fee. Tetraphase: Consultant, Consulting fee. Theravance: Consultant, Consulting fee. Wockhardt: Consultant, Consulting fee. **P. Eckburg**, Paratek: Consultant, Consulting fee. **P. McGovern**, Paratek Pharmaceuticals: Employee, Salary.

1348. *In vitro* Activity of Plazomicin, a Next-Generation Aminoglycoside, Against Carbapenemase-Producing *Klebsiella pneumoniae*

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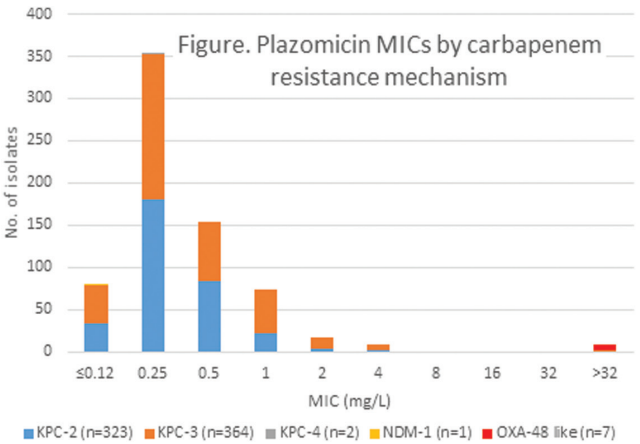
Background. Plazomicin is a next-generation aminoglycoside with *in vitro* activity against multidrug-resistant Gram-negative species, including carbapenem-resistant isolates. The Consortium on Resistance Against Carbapenems in Klebsiella and other Enterobacteriaceae (CRACKLE) is a federally funded, prospective multicenter consortium of 20 hospitals from nine US healthcare systems to track carbapenem-resistant Enterobacteriaceae.

Methods. Minimum inhibitory concentrations (MICs) of plazomicin were determined by broth microdilution according to current CLSI guidelines against a collection of 697 carbapenem-resistant *Klebsiella pneumoniae* with defined carbapenem resistance mechanisms, including KPC and OXA carbapenemases. Isolates were submitted by participating CRACKLE centers.

Results. Carbapenemases present in study isolates included KPC-2 ($n = 323$), KPC-3 ($n = 364$), KPC-4 ($n = 2$), OXA-48 like ($n = 7$), and NDM ($n = 1$). Plazomicin MICs ranged from ≤0.12 to >32 mg/L, with MIC50 and MIC90 values of 0.25 and 1 mg/L, respectively (figure). MICs of 689 (98.8%) isolates were ≤4 mg/L, while MICs of the remaining eight isolates were >32 mg/L. Plazomicin MICs were related to specific carbapenemases present in isolates: of eight isolates with MICs >32 mg/L, seven contained OXA-48 like and one contained KPC-3, suggesting that these isolates possess an aminoglycoside-resistance mechanism on the same plasmid as their carbapenemase gene, such as a 16S ribosomal RNA methyltransferase, against which plazomicin is not active.

Conclusion. Plazomicin has good *in vitro* potency against a collection of carbapenemase-producing *K. pneumoniae*, with MIC90 value of 1 mg/L and MICs of ≤4 mg/L for 98.9% of isolates.



Disclosures. **M. R. Jacobs**, Achaogen: Investigator, Research grant. Shionogi: Investigator, Research grant. **L. Connolly**, Achaogen, Inc.: Consultant, Consulting

fee. **K. M. Krause**, Achaogen: Employee, Salary. **S. S. Richter**, bioMerieux: Grant Investigator, Research grant. BD Diagnostics: Grant Investigator, Research grant. Roche: Grant Investigator, Research grant. Hologic: Grant Investigator, Research grant. Diasorin: Grant Investigator, Research grant. Accelerate: Grant Investigator, Research grant. Biofire: Grant Investigator, Research grant. **D. Van Duin**, achaogen: Scientific Advisor, Consulting fee. shionogi: Scientific Advisor, Consulting fee. Allergan: Scientific Advisor, Consulting fee. Astellas: Scientific Advisor, Consulting fee. Neumedicine: Scientific Advisor, Consulting fee. Roche: Scientific Advisor, Consulting fee. T2 Biosystems: Scientific Advisor, Consulting fee.

1349. Global Surveillance of Cefiderocol Against Gram-Negative Clinical Strains Collected in North America: SIDERO-WT-2015

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Background. Cefiderocol (CFDC) is a novel parenteral siderophore cephalosporin with potent activity against a wide range of Gram-negative pathogens, including carbapenem-resistant strains. Additionally, a recently conducted *in vivo* murine-based study has demonstrated an incremental exposure-response profile over a dose range without the appearance of adaptive resistance. In this study, we evaluated the *in vitro* activity of CFDC and comparator agents against clinical isolates collected in 2015–2016 from North America from SIDERO-WT-2015 surveillance study.

Methods. A total of 3,602 isolates (2,470 *Enterobacteriaceae*, 223 *A. baumannii*, 85 *Acinetobacter* spp., 619 *P. aeruginosa*, 165 *S. maltophilia* and 17 *Burkholderia* cepacia, and 23 *Burkholderia* spp.) collected from the United States and Canada in 2015–2016 were tested. MICs were determined for CFDC, cefepime (FEP), ceftazidime–avibactam (CZA), ceftolozane–tazobactam (C/T), ciprofloxacin (CIP), colistin (CST), and meropenem (MEM) by broth microdilution and interpreted according to CLSI guidelines. As recommended by CLSI, cefiderocol was tested in iron-depleted cation-adjusted Mueller–Hinton broth (ID-CAMHB). Carbapenem nonsusceptible (Carb-NS) strains were defined as MEM MIC ≥2 μg/mL for *Enterobacteriaceae*, and ≥4 μg/mL for nonfermenters.

Results. CFDC exhibited potent *in vitro* activity against 3,602 strains of Gram-negative bacteria with an overall MIC_{90} of 0.5 mg/mL. As shown in the following table, MIC_{90} of CFDC against *P. aeruginosa*, *A. baumannii*, *S. maltophilia*, and *Enterobacteriaceae* including the subset of Carb-NS isolates were 0.5, 2, 0.5 and 0.5 mg/mL, respectively. At 4 mg/mL, CFDC inhibited the growth of 99.6% of the isolates while 18.1%, 12.6%, and 13.8% showed resistance to CZA, C/T, and CST, respectively.

Conclusion. CFDC demonstrated potent *in vitro* activity against the teat isolates collected from North America with greater than 99.6% of isolates having MIC values ≤4 mg/mL, including Carb-NS isolates of *A. baumannii*, *P. aeruginosa*, and *Enterobacteriaceae*. These findings indicate that this agent has high potential for treating infections caused by these problematic organisms.

Organisms	N	CFDC	FEP	CZA	C/T	CIP	CST	MEPM
Enterobacteriaceae	2470	0.5	4	0.5	1	>8	>8	≤0.06
P. aeruginosa	619	0.5	16	8	2	>8	2	8
A. baumannii	223	2	>64	>64	>64	>8	1	>64
S. maltophilia	165	0.5	>64	64	>64	>8	8	>64

Disclosures. **M. Tsuji**, Shionogi & Co., Ltd.: Employee, Salary. **M. Hackel**, IHMA, Inc.: Employee, Salary. **Y. Yamano**, Shionogi & Co., Ltd.: Employee, Salary. **D. Sahm**, IHMA, Inc.: Employee, Salary.

1350. Therapeutic Effects of Baloxavir Marboxil against Influenza A Virus Infection in Ferrets

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Background. Baloxavir marboxil (BXM) is a novel small molecule inhibitor of cap-dependent endonuclease that is essential for influenza virus transcription and replication. In this study, pharmacokinetic profiles of BXM and baloxavir acid (BXA), an active form of BXM, were first examined in ferrets, and then the therapeutic effects of BXM against influenza A virus infection were compared with that of oseltamivir phosphate in ferrets.

Methods. The plasma exposure of BXA and BXM was examined after a single oral administration of BXM at doses of 10 and 30 mg/kg. The concentrations in plasma were determined by liquid chromatography-tandem mass spectrometry(LC/MS/MS). For efficacy study, ferrets infected intranasally with A/Kadoma/2006 (H1N1) were administrated 10 or 30 mg/kg of BXM orally twice daily for 1 day, starting at 1 day post-infection (p.i.) or administrated 10 mg/kg of BXM orally twice daily for 1 day, starting at 2 days p.i.. Oseltamivir phosphate was administered at doses of 5 mg/kg orally twice daily for 2 days as a comparison. The virus titer in the nasal washes and body temperature change were monitored during infection.

Results. BXA was detected in ferret plasma after a single oral administration of BXM at 10 and 30 mg/kg, in more than a dose-proportional manner. When the treatment was initiated at 1 day p.i., BXM at 10 and 30 mg/kg showed reduction of virus titer to an undetectable level on day 2 p.i. and statistically significant reduction in virus titer over time from day 2 to 3 p.i. compared with vehicle and oseltamivir phosphate. Moreover, the change of body temperature over time from 8 hours after the first administration to 3 days p.i. was significantly lower in BXM at 10 and 30 mg/kg than vehicle and oseltamivir phosphate. These effects were also observed in ferrets treated with BXM at 10 mg/kg even when administered at 2 day p.i. where ferret exhibit fever that is more than 1 degree higher than on 1 day p.i..

Conclusion. Single-day oral administration of BXM had beneficial effects on viral titer and symptoms in ferrets infected with influenza A virus, which were superior to those observed with oseltamivir phosphate and vehicle.

Disclosures. **M. Kitano**, Shionogi & Co., Ltd.: Employee, Salary. **T. Matsuzaki**, Shionogi & Co., Ltd.: Employee, Salary. **R. Oka**, Shionogi & Co., Ltd.: Employee, Salary. **K. Baba**, Shionogi TechnoAdvance Research & Co., Ltd.: Employee, Salary. **T. Noda**, Shionogi TechnoAdvance Research & Co., Ltd.: Employee, Salary. **Y. Yoshida**, Shionogi & Co., Ltd.: Employee, Salary. **K. Sato**, Shionogi & Co., Ltd.: Employee, Salary. **R. Yoshida**, Shionogi & Co., Ltd.: Employee, Salary. **A. Sato**, Shionogi & Co., Ltd.: Employee, Salary. **H. Kamimori**, Shionogi & Co., Ltd.: Employee, Salary.

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1351. *In vitro* Activity of Cefiderocol (S-649266), a Siderophore Cephalosporin, Against Enterobacteriaceae With Defined Extended-Spectrum B-Lactamases and Carbapenemases

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Background. Cefiderocol is a novel siderophore cephalosporin targeted for activity against carbapenem and multidrug-resistant Gram-negative species, including extended-spectrum β-lactamase (ESBL) and carbapenemase-producing strains. The Consortium on Resistance Against Carbapenems in Klebsiella and other Enterobacteriaceae (CRACKLE) is a federally funded, prospective multi-center consortium of 20 hospitals from nine US healthcare systems to track carbapenem-resistant Enterobacteriaceae.

Methods. Minimum inhibitory concentrations (MICs) of cefiderocol and meropenem were determined by broth microdilution according to current CLSI guidelines. Cefiderocol was tested in iron-depleted cation-adjusted Mueller–Hinton (MH) broth, meropenem was tested in cation-adjusted MH broth. Cefiderocol MICs were read as the first drug well in which the growth was significantly reduced (i.e., a button of <1 mm or light/faint turbidity) relative to the growth observed in the growth control well containing the same medium. Trailing endpoints were disregarded. Isolates tested included 35 *Escherichia coli*, five Enterobacter/Citrobacter group, and 794 *Klebsiella pneumoniae*. Isolates had characterized β-lactamases including TEM, SHV, and CTX-M ESBLs and KPC, NDM, and OXA carbapenemases.

Results. Cefiderocol MICs ranged from ≤0.03 to >64 mg/L, with overall MIC50 of 0.5 mg/L and MIC90 of 4 mg/L (table). MIC90 value (≤0.03 mg/L) was lowest against isolates with no ESBLs or carbapenemases. MIC90 was 1 mg/L for OXA and TEM/SHV groups, 2–4 mg/L for KPC-3 groups and 8 mg/L for NDM and KPC-2 groups.

Conclusion. Compared with isolates without ESBLs and carbapenemases, cefiderocol shows higher MICs against isolates with ESBLs, including TEM, SHV, and CTX-M and carbapenemases including KPC, NDM, and OXA. The clinical utility of cefiderocol against ESBL and carbapenemase-producing *Enterobacteriaceae* is dependent on the pharmacokinetic and pharmacodynamic properties of cefiderocol.

Table: Activity of Cefiderocol

β-Lactam Resistance	N	MIC range (mg/L)	MIC50 (mg/L)	MIC90 (mg/L)
ampC	3	0.25 to 2	NA	NA
KPC-2	255	≤0.03 to 32	0.5	8
KPC2 + Other	101	≤0.03 to 16	2	8
KPC-3	276	≤0.03 to 64	0.25	2
KPC3 + Other	106	≤0.03 to 16	0.5	4
NDM	28	0.25 to >64	2	8
OXA	8	≤0.03 to 1	0.25	1
TEM/SHV ESBL	42	≤0.03 to >64	2	1
None	15	≤0.03 to 0.12	≤0.03	≤0.03
All	834	≤0.03 to >64	0.5	4