Conclusion. WCK 4282, a novel TZB containing regimen, resulted in enhance *in vitro* potency against ESBL/CSase and OXA-48-like producers. Humanized exposures of WCK 4282 produced substantial kill *in vivo* against ESBL/CSase producers with MICs ≤ 16 mg/L including FEP resistant/TZP non-susceptible PA. These data support further evaluations of WCK 4282 as a carbapenem-sparing regimen for ESBL/cephalosporinase harboring strains.

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1245. *In Vivo* Efficacy of WCK 4282 (High Dose Cefepime [FEP]-Tazobactam [TZB]) Against β-Lactamase-Producing (BLP) Gram-Negative Bacteria in a Neutropenic Murine Pneumonia Model

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Session: P-58. Novel Agents

Background. Carbapenems are often used for Extended-Spectrum β-lactamase (ESBL)- and cephalosporinase (AmpC or CMY)-producing infections. Their increased use resulted in the emergence of carbapenem resistance among Gram-negatives, promoting the need of an effective carbapenem-sparing option. WCK 4282 (FEP 2g-TZB 2g) maximizes systemic exposure of TZB and restores FEP activity against piperacillin-tazobactam (TZP) resistant isolates *in vitro*. Herein we describe the efficacy of WCK 4282 clinical exposures against BLP Enterobacterales (EB) and *Pseudomonas aeruginosa* (PA) in a murine pneumonia model.

Methods. Clinical isolates (14 EB and 2 PA) with *in vitro* resistance to FEP, ceftolozane-tazobactam, and TZP (EB isolates) were used. Isolates expressed ESBLs, AmpC/CMY, and/or serine carbapenemases (KPC, OXA-48-like). WCK 4282 MICs were 4-16 and 8-32 mg/L for non-carbapenemase and carbapenemase-producers, respectively. Human-simulated regimens (HSR) of FEP (mimicking human plasma exposure of 2g q8h as a 1.5 h infusion) alone and in combination with TZB (equivalent to 2g q8h as a 1.5 h infusion) were developed in a neutropenic pneumonia model. Treatment mice received FEP or FEP-TZB (WCK 4282) HSR. Control mice were vehicle-dosed. Efficacy was assessed as change in $\log_{10}$CFU/lung at 24 h compared with 0 h controls.

Results. Mean 0 h bacterial density across all isolates was 6.66 ± 0.29 $\log_{10}$CFU/lung and increased at 24 h by 2.48 ± 0.6 and 1.71 ± 1.13 among controls and FEP-treated groups, respectively. Potent WCK 4282 activity was observed against ESBL- and AmpC-harboring EB as well as ESBL- and AmpC-overexpressing PA with WCK 4282 MICs up to 16 mg/L (n=9); mean bacterial reductions were -2.70 ± 0.63 and -2.04 ± 0.18 $\log_{10}$CFU/lung, respectively. WCK 4282 showed variable activity against OXA-48-producing EB (n=3); $\log_{10}$CFU/lung change ranged from -1.2 to 0.28. Against KPC-producers (n=4), WCK 4282 groups grew to 0.53 ± 1.07 $\log_{10}$CFU/lung, ~1.2 $\log_{10}$CFU lower than FEP.

Conclusion. WCK 4282 produced potent *in vivo* activity against ESBL- and AmpC-harboring Gram-negative isolates and limited activity among serine carbapenamase-producers in a pneumonia model at clinically achievable exposures. Further studies are warranted to delineate WCK 4282's spectrum of activity and susceptibility breakpoint.

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1247. Dalbavancin in Osteomyelitis and Joint Infections: An Analysis From an Observational, Multicenter, Retrospective Cohort Study of the Real-World Use in Adult Patients

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Background. Dalbavancin (DAL) is approved in the United States (US) and Europe for acute bacterial skin and skin structure infections and exhibits broad spectrum activity against clinically important Gram-positive pathogens including methicillin-sensitive and methicillin-resistant *Staphylococcus aureus*, and *Streptococcus* spp. We describe the use of DAL in patients with osteomyelitis or joint infection from a phase 4 observational, multicenter, retrospective cohort study of the real-world use of DAL in adult patients across the US: Dalvance Utilization Registry Investigating Value and Efficacy (DRIVE).

Methods. Data were collected between 03/25/2017 and 11/27/2018 and included demographics, disease and pathogen characteristics, antibiotic use, clinical outcome, and safety. Patients with a determinate clinical outcome (success/failure) were included in the evaluable population.

Results. Data for 96 patients with osteomyelitis and 33 patients with joint infection (safety population) were entered into this subanalysis. Patient demographics and medical history were broadly similar for patients with osteomyelitis or joint infection. The majority (80.4–100%) of patients received DAL as concurrent therapy and clinical success, defined qualitatively, was achieved in 64.7-87.5% of patients (**Fig. 1**). Most patients received 1 or 2 IV DAL doses (osteomyelitis, 33.3% and 34.6%, respectively; joint infection, 37.5% and 31.3%, respectively); 11.5% and 6.3% of patients with osteomyelitis or joint infection, respectively received >4 doses (**Fig. 2**). *Staphylococcus* spp. was the most frequently isolated organism at baseline (**Fig. 3**); 61.1% and 35.7% of osteomyelitis and joint infection isolates tested, respectively were resistant to oxacillin. At 60 days post-DAL treatment, numbers of *Staphylococcus* spp. isolated from both groups decreased **(Fig. 3)**, confirming microbiological cure. The rate of serious adverse events was low (16 events in 7 [7.3%] patients with osteomyelitis, 2 events in 2 [6.1%] patients with joint infection) and consistent with the safety profile of DAL.

Fig. 1

Fig.1: Final Diagnosis and Clinical Outcome – Dalbavancin as Mono- or Concurrent Therapy (Evaluable Population)

		Dalbavancin Use			
Final Diagnosis	**Clinical Success (n/N, %) [95% CI]***	**Monotherapy, n (%)**	**Concurrent Therapy, n (%)**	**Clinical Success With Monotherapy, n (%)**	**Clinical Success With Concurrent Therapy, n (%)**
Osteomyelitis					
All patients (n=78)	63 (80.8) [70.3 to 88.8]	11 (14.1)	67 (85.9)	9 (81.8) [48.2 to 97.7]	54 (80.6) [69.1 to 89.2]
Osteomyelitis of the foot (n=51)	43 (84.3) [71.4 to 93.0]	10 (19.6)	41 (80.4)	8 (80.0) [44.4 to 97.5]	35 (85.4) [70.8 to 94.4]
Osteomyelitis of upper body sites † (n=17)	11 (64.7)	0 (0.0)	17 (100.0)	0 (0.0)	11 (64.7)
Osteomyelitis of lower body sites† (n=10)	9 (90.0)	1 (10.0)	8 (88.9)	1 (100.0)	7 (87.5)
Joint infection					
All patients (n=32)	28 (87.5) [71.0 to 96.5]	4 (12.5)	28 (87.5)	4 (100.0)	24 (85.7) [67.3 to 96.0]
Knee (n=10)	8 (80.0) [44.4% to 97.5%]	1 (10.0)	9 (90.0)	1 (100.0)	7 (77.8) [40.0 to 97.2]

*Where available. †Upper body=skull, spine, thorax/ribs, hand, forearm, arm, shoulder; lower body=leg, thigh, hip, pelvis

Fig. 2

Fig. 2: Number of Intravenous Dalbavancin Doses Received (Evaluable Population)