Conclusion. There was no difference in risk for AEs or lab abnormalities between PfSPZ Vaccine and NS, indicating that PfSPZ Vaccine administered by DVI was extremely safe and well tolerated in 5-month- to 65-year-olds.

Disclosures. LW Preston Church, MD, FIDSA, Sanaria Inc. (Employee)

1242. Safety and Immunogenicity of Novel 24-Valent Pneumococcal Vaccine in Healthy Adults

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Session: P-57. New Vaccines

Background. Invasive pneumococcal disease (IPD) remains prevalent despite the use of conjugate vaccines over the past 20 years. Serotype replacement, limited efficacy for certain vaccine serotypes, and the incomplete coverage of disease in the elderly perpetuate the problem. Novel vaccines with broader serotype coverage are needed. To this end, a novel 24-valent pneumococcal vaccine, ASP3772, was developed based on a multiple antigen-presenting system (MAPS) platform. This platform takes advantage of the high affinity, noncovalent binding between biotin and rhizavidin to create a complex of 24 pneumococcal polysaccharides and a fusion of two pneumococcal proteins.

Methods. Healthy adults aged 18-64 years were randomized into this active-controlled, observer-blinded, dose-escalation study to evaluate the safety, tolerability, and immunogenicity of ASP3772 at three dose levels compared to Prevnar13 (PCV13) (target 30 per dose group). The primary endpoints were safety and reactogenicity. Immunogenicity was evaluated secondarily by measuring serotype-specific immunoglobulin G (IgG) and opsonophagocytic activity (OPA).

Results. Ninety-three subjects received ASP3772 at 1 of 3 doses and 33 received PCV13. Safety and reactogenicity were similar between the ASP3772 and PCV13 arms. Most frequently reported local reactions were tenderness and pain after injection occurring within the first 2 days. Most frequent systemic reactions were fatigue, headache, and myalgia, without a clear dose response. Treatment-emergent adverse events were few and most were mild to moderate in severity. No clinically relevant abnormalities were observed in vital signs, ECGs, and laboratory parameters. Robust IgG and OPA responses were observed for serotypes shared with PCV13, as well as serotypes unique to ASP3772.

Conclusion. ASP3772 vaccine was safe, well tolerated in adults aged 18-64 years, and exhibited robust immunogenicity that extended beyond serotypes shared with PCV13.

Disclosures. Gurunadh Chichili, PhD, Astellas Pharma Inc (Employee) Ronald Smulders, MD, PhD, Astellas Pharma Inc (Employee) Vicki Santos, n/a, Astellas Pharma Inc (Employee) Beth Cywin, n/a, Astellas Pharma Inc (Employee) Laura Kovanda, n/a, Astellas Pharma Inc (Employee) Frank J. Malinoski, MD, PhD, Affinivax Inc (Employee) Shite Sebastian, PhD, Affinivax Inc (Employee) George R. Siber, MD, Affinivax Inc (Consultant, Employee, Shareholder) Rick Malley, MD, Affinivax Inc (Board Member, Consultant, Employee)

1243. Semi-Quantitative Benefit-Risk Assessment for a New Quadrivalent Meningococcal Conjugate Vaccine (MenACYW-TT) in Individuals 2 Years of Age and Older

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Session: P-57. New Vaccines

Background. MenACYW-TT is a new quadrivalent meningococcal conjugate vaccine approved by the US FDA for use in individuals 2 years and older. We present the structured benefit-risk assessment conducted by Sanofi Pasteur in support of the initial biological license application for MenACYW-TT.

Methods. The safety and immunogenicity of MenACYW-TT in subjects ≥ 2 years was evaluated in 5 pivotal randomized, active-controlled clinical trials. Collectively, 4,919 subjects received either a single primary dose (n=4517) or a booster dose (n=402) of MenACYW-TT. A semi-quantitative framework was used to establish favorable and unfavorable effects of MenACYW-TT relative to comparators: MenACWY-CRM in children 2-9 years and adolescents 10-17 years, MenACWY-D in adolescents 10-17 years and adults 18-55 years, and MPSV4 in older adults ≥ 56 years. Benefit outcome measures included vaccine seroresponse and seroprotection (titers ≥ 1:8) at D30 evaluated by serum bactericidal assay using human complement, for each serogroup. Risk outcome measures included rates of solicited injection site and systemic reactions (including grade 3 reactions) within 7 days after vaccination, and rates of serious adverse events within 6 months after vaccination. The differences in rates for MenACWY-TT vs comparator vaccines were calculated along with 95% confidence intervals.

Results. For all benefit criteria, and in all age groups, rate differences favored MenACYW-TT in meningococcal vaccine-naïve individuals. Immune response differences were more pronounced for serogroup C. Differences showed favorable (seroresponse criteria) or comparable (seroprotection criteria) effects for MenACYW-TT in adolescents and adults previously primed with MenACWY-D or MenACWY-CRM. For the risk criteria, rate differences generally showed comparable effects between MenACYW-TT and MenACWY-D or MenACWY-CRM in children, adolescents and adults, while the rate differences for both solicited injection site and systemic reactions favored MPSV4 in older adults. The latter was possibly due to the use of a protein carrier in MenACYW-TT.

Conclusion. The benefit risk-profile of MenACYW-TT in individuals ≥ 2 years is considered favorable relative to comparator licensed vaccines.

Disclosures. David Neveu, MPharm, Sanofi Pasteur (Employee) Marie-Laure Kürzinger, MSc, Sanofi (Employee) Aiying Chen, PhD, Sanofi Pasteur (Employee) Mandeep S. Dhingra, MD, Sanofi Pasteur (Employee)

1244. Assessment of the *In Vivo* Activity of Human-Simulated Exposure of WCK 4282 (High Dose Cefepime [FEP]-Tazobactam [TZB]) against *Enterobacterales* (EB) and *Pseudomonas aeruginosa* (PA) in the Neutropenic Murine Thigh Infection Model

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Session: P-58. Novel Agents

Background. Carbapenems are often used for infections due to extended-spectrum-β-lactamase (ESBL) and cephalosporinase (CSase)-producers. As increased carbapenem utilization is associated with the development of carbapenem resistance, antimicrobial stewardship has targeted non-carbapenem options. WCK 4282 (FEP 2 g-TZB 2 g) offers pharmacodynamically optimized TZB exposure and demonstrated potent activity *in vitro* against ESBL-phenotype isolates. We describe the pharmacodynamics of a WCK 4282 human-simulated regimen (HSR) in the neutropenic murine thigh model.

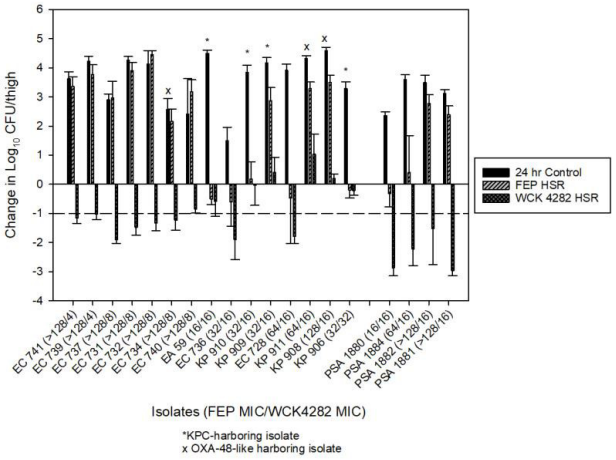
Methods. 19 clinical strains harboring ESBLs or CSase (EB; n=8 and PA; n=4) or serine-carbapenemases (EB; KPC n=4 or OXA-48-like n=3) were tested in vivo. Per CLSI, 19, 18, and 17 isolates were cefepime, ceftolozane/tazobactam, and piperacillin/tazobactam (TZP) non-susceptible, respectively. Thighs of neutropenic, female, CD-1 mice (3 per group) were inoculated with ~10^7 CFU/mL of bacterial suspension 2 h prior to dosing. Mice received WCK 4282 HSR, FEP HSR, or saline (controls) for 24 h. WCK 4282 HSR and FEP HSR provided plasma exposures in mice that were similar in *f*%T > MIC and *f*AUC to FEP-TZB 2 g-2 g and FEP 2 g, respectively, as IV infusions over 1.5 h q8h in humans. Bacterial densities and their changes at 24 h relative to 0 h controls were determined to assess efficacy and reported as mean±SD $\log_{10}$ CFU/thigh.

Results. Bacterial burdens were 5.81±0.36 at 0 h and 9.29±0.88 at 24 h in untreated controls. WCK 4282 produced potent activity against ESBL/CSase producing EB and PA with WCK 4282 MIC ≤ 16 mg/L; mean change in $\log_{10}$ CFU from 0 h was -1.70±0.77, while growth was observed with FEP alone. WCK 4282 produced variable activity against OXA-48-like harboring EB. Against KPC-harboring EB, WCK 4282 produced stasis to growth. Mean Log_{10} CFU changes are reported in **Table 1** and **Figure 1**.

Table 1. Comparative efficacy of FEP HSR and WCK 4282 HSR by genotypic β-lactamase

β-lactamase Class	Organism	Number of Isolates	FEP MIC Range (mg/L)	WCK 4282 MIC range fixed TZB 8 mg/L (mg/L)	FEP HSR Mean $\text{Log}_{10}\Delta$ CFU/Thigh	WCK 4282 HSR Mean $\text{Log}_{10}\Delta$ CFU/Thigh
ESBL/CSase	*Enterobacterales*	8	32 - >128	4 - 16	2.06±2.16	-1.44±0.52
	P. aeruginosa	4	16- >128	16	1.32±1.49	-2.40±0.88
KPC	*Enterobacterales*	4	16 - 32	16 - 32	0.59±1.41	-0.1±0.61
OXA-48-like	*Enterobacterales*	3	64 - >128	8 - 16	2.98±0.67	0.00±1.06

Figure 1. Mean Change in log10CFU/thigh for 24 h controls, FEP HSR, and WCK 4282 HSR across the tested MIC distribution.



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.

Disclosures. **David P. Nicolau, PharmD**, **Cepheid** (Other Financial or Material Support, Consultant, speaker bureau member or has received research support.)**Merck & Co., Inc.** (Consultant, Grant/Research Support, Speaker's Bureau)**Wockhardt** (Grant/Research Support)

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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Session: P-58. Novel Agents

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)