Methods. Eight isolates (1 MSSA and 7 MRSA) were studied. Murine ICR MIC (100% serum) and human MIC (100% serum) for CF-296 ranged from 32-256 mg/L to 0.5-1 mg/L respectively. Broth microdilution MICs for DAP ranged from 0.5-1 mg/L while all isolates exhibited a VAN MIC of 1 mg/L. Neutropenic ICR mice were thigh inoculated with bacterial suspensions (10^7 CFU/mL). Mice were administered three monotherapy regimens subcutaneously (SC) or intravenously (IV): i) sub-therapeutic VAN, SC (i.e., a dose that yielded bacteria stasis or growth in order to evaluate further bacterial killing), ii) sub-therapeutic DAP, SC, or iii) CF-296 50 mg/kg, IV. Combination of sub-therapeutic VAN or DAP in addition to 5 escalating CF-296 doses ranging from 0.5 to 50 mg/kg were also examined. Control mice were vehicle-dosed. Efficacy was measured as the change in mean thigh bacterial density at 24h relative to 0h controls.

Results. Relative to starting inoculum (5.71 ± 0.27 at 0h), bacterial density in controls increased by +2.49 ± 0.98 $\log_{10}$ CFU/thigh across all 8 strains. On average, VAN, DAP, and CF-296 monotherapy resulted in +0.90 ± 1.21, +1.47 ± 0.80, and +0.87 ± 1.39 $\log_{10}$ CFU/thigh bacteria growth, respectively. In addition to VAN, escalating CF-296 exposures (0.5 – 50 mg/kg) resulted in an augmented dose-response, ranging from bacterial reduction of -0.26 ± 1.10 (with addition of CF-296 0.5 mg/kg) to -1.01 ± 0.41 $\log_{10}$ CFU/thigh (with addition of CF-296 50 mg/kg). Similarly, escalating CF-296 exposures in addition to DAP resulted in an augmented dose-response, ranging from bacterial density of +0.80 ± 1.19 to -0.72 ± 0.59 $\log_{10}$ CFU/thigh.

Conclusion. Compared with 24h control, VAN, DAP, and CF-296 alone displayed modest CFU reduction while CF-296 synergized with VAN and DAP to cause further bacterial killing highlighting a potential role for CF-296 adjunctive therapy against MSSA and MRSA isolates.

Disclosures. Cara Cassino, MD, ContraFect Corporation (Employee)ContraFect Corporation (Employee) Dario Lehoux, PhD, ContraFect Corporation (Consultant) Raymond Schuch, PhD, ContraFect Corporation (Employee) 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)

1265. AT-527, an Oral Purine Nucleotide Prodrug Exhibiting Potent In Vitro Antiviral Activity Against Human Coronaviruses, Including SARS-CoV-2

Steven S. Good, MS[1]; Adel Moussa, PhD[1]; Xiao-Jian Zhou, PhD[1]; Keith Pietropaolo, B.A.[1]; Jean-Pierre Sommadossi, PhD[1]; [1]Atea Pharmaceuticals, Inc., Boston, Massachusetts

Session: P-58. Novel Agents

Background. Coronaviruses (CoVs) are the causative pathogens of several human diseases, including seasonal respiratory infections (HCoV-229E and HCoV-OC43), Middle East respiratory syndrome (MERS-CoV), severe acute respiratory syndrome (SARS-CoV-1) and the novel CoV recently identified as the virus responsible for the current COVID-19 pandemic, SARS-CoV-2. AT-527 is currently in Phase 2 clinical trials and has demonstrated potent activity and a well-tolerated safety profile in HCV-infected subjects. Here we report the *in vitro* activity of AT-511, the free base form of AT-527, against SARS-CoV-2 and other CoVs.

Methods. BHK-21, Huh-7, RD and differentiated normal human bronchial epithelial (dNHBE) cell cultures were exposed to virus and serial dilutions of test compounds. Independent assessments of antiviral activity were obtained by determining effective concentrations of test compounds required to 1) prevent half-maximal (EC_{50}) virus-induced cytopathic effect (CPE) using MTT or neutral red staining and 2) produce virus yield reductions (VYR) by 90% (EC_{90}) using standard endpoint dilution $CCID_{50}$ assays in Vero 76 cells. Half maximal cytotoxicity of test compounds was determined by dye (MTT or neutral red) staining in the absence of added virus or by microscopic inspection (dNHBE cells only).

Results. Table 1 presents the *in vitro* activities of AT-511 against several coronaviruses. Also included in these assays are the antiviral activities of potential COVID-19 oral treatments, including chloroquine, hydroxychloroquine and N^4-hydroxycytidine.

Table 1. In Vitro Activity of AT-511 Against Various Human Coronaviruses

Virus (genus)	Cell line	Compound	Neutral Red Assay		Virus Yield Reduction Assay	Selectivity Index
			EC_{50} (μM)	CC_{50} (μM)	EC_{90} (μM)	(CC_{50}/EC_{90})
HCoV-229E (alpha)	BHK-21	AT-511	1.8[a,b]	>100		>58[c]
		sofosbuvir	>100[b]	>100		N/A
	Huh-7	AT-511	1.7 / 1.6	>86	1.0	>75
		chloroquine	8.1	21	<0.050	2.6[c]
		hydroxychloroquine	7.4	26	<0.048	3.5[c]
HCoV-OC43 (beta)	Huh-7	AT-511	ND[d]	>86	0.5 / <0.03	>170 / >3100
	RD	AT-511	2.8	>86	2.2	>39
MERS-CoV (beta)	Huh-7	AT-511	15 / 36	>86	17 / 56	>5 / >1.5
SARS-CoV-1 (beta)	Huh-7	AT-511	ND	>86	0.34	>250
SARS-CoV-2 (beta)	dNHBE	AT-511	ND	>86[e] / >8.6[e]	0.64[f] / 0.47[g]	>130 / >18
		N^4-hydroxycytidine		>19[e]	3.9[h]	>5.1

[a]Average of 2 experiments (1.6 and 2.0 μM)
[b]EC_{50} determined by dye staining (virus yield reduction substantially overestimates antiviral potency of cytotoxic compounds)
[c]CC_{50}/EC_{90}
[d]Not determined (no cytopathic effect with this virus in this cell line)
[e]Cytotoxicity assessed by visual inspection of cell monolayers
[f]Average of two replicates (0.57 and 0.70 μM)
[g]Average of two replicates (0.52 and 0.42 μM)
[h]Average of two replicates (4.7 and 3.1 μM)
BHK-21, baby hamster kidney cell line
Huh-7, human hepatocyte carcinoma cell line (established ability to form triphosphate from AT-511)
RD, human rhabdomyosarcoma cell line (unknown ability to form triphosphate from AT-511)
dNHBE, differentiated normal human bronchial epithelial cell preparation (established ability to form triphosphate from AT-511)

Conclusion. The data demonstrate the potent *in vitro* activity of AT-511 against several CoVs, with individual EC_{90} values ranging from 0.34 to 1.2 μM against HCoV-229E, HCoV-OC43, SARS-CoV-1 and SARS-CoV-2 and less activity against MERS-CoV (average EC_{90} = 36 μM). The potent *in vitro* antiviral activity of AT-511 against SARS-CoV-2 (EC_{90} = 0.55 μM), associated with the AT-527 safety profile in treated HCV patients, support the ongoing clinical evaluation of the safety and efficacy of AT-527 in COVID-19 patients.

Disclosures. Steven S. Good, MS, Atea Pharmaceuticals, Inc. (Employee) Adel Moussa, PhD, Atea Pharmaceuticals, Inc. (Employee) Xiao-Jian Zhou, PhD, Atea Pharmaceuticals, Inc. (Employee) Keith Pietropaolo, B.A., Atea Pharmaceuticals, Inc. (Employee) Jean-Pierre Sommadossi, PhD, Atea Pharmaceuticals, Inc. (Board Member)

1266. Characterization of Shifts in Minimum Inhibitory Concentrations During Treatment with Cefiderocol or Comparators in the Phase 3 CREDIBLE-CR and APEKS-NP Studies

Miki Takemura, MSc[1]; Yoshinori Yamano, PhD[1]; Yuko Matsunaga, MD[2]; Mari Ariyasu, BPharm[1]; Roger Echols, MD[3]; Tsutae Den Nagata, MD[1]; [1]Shionogi & Co., Ltd., Osaka, Osaka, Japan; [2]Shionogi Inc., Florham Park, New Jersey; [3]Infectious Disease Drug Development Consulting LLC, Easton, Connecticut

Session: P-58. Novel Agents

Background. Cefiderocol (CFDC) is a novel siderophore cephalosporin developed to treat serious carbapenem-resistant (CR) Gram-negative (GN) infections.

Methods. In CREDIBLE-CR (NCT02714595), adults with serious infections caused by CR GN pathogens received CFDC 2 g, q8h, 3-h infusion, or best available therapy (BAT). In APEKS-NP (NCT03032380), adults with nosocomial pneumonia received CFDC or high-dose, extended-infusion meropenem (each 2 g, q8h, 3-h infusion). All treatments were given for 7–14 days (extendable to 21 days). Biospecimens were collected before the first dose of study drug and at subsequent visits for assessments, and minimum inhibitory concentrations (MIC) to various antibiotics, including CFDC and carbapenems, were determined. Isolates with an increased MIC were evaluated by RT-PCR or whole genome sequencing (WGS) for CFDC resistance-related genes or mutations. Results for genetically related isolates with an elevated MIC during therapy are shown.

Results. On-therapy ≥4-fold CFDC MIC increase was found in 12 out of 106 (CREDIBLE-CR; Table 1) and 7 out of 159 (APEKS-NP; Table 2) isolates, respectively. For most isolates, CFDC MIC increased by 4–8-fold but remained ≤4 μg/mL. Specific mutations which could explain CFDC MIC increases were found in only 3 isolates. Mutations in iron-transport related genes were not identified. Mutation in CFDC target gene PBP-3 was identified in 1 *A. baumannii* isolate. Class-C enzyme mutation was observed in 2 isolates (CREDIBLE-CR: PDC-30 in *P. aeruginosa*; APEKS-NP: ACT-17 in *E. cloacae*), although the contribution to CFDC MIC increase has not been confirmed. In the BAT arm in CREDIBLE-CR, 6 out of 46 isolates had ≥4-fold MIC increase; all post-treatment isolates were resistant to BAT agents (Table 1), although WGS was not conducted for these isolates. In the meropenem arm in APEKS-NP, 5 out of 164 isolates had ≥4-fold MIC increase (Table 2).

Table 1. MIC changes in CREDIBLE-CR

Table 1. MIC changes in CREDIBLE-CR

Isolate	MIC (μg/mL)		Fold change of MIC	Mutation identified the post-treatment isolates
	Pre-treatment*	Post-treatment		
Cefiderocol arm				
A. baumannii	0.06	1	16	
	0.25	1	4	
	0.25	2	8	
	1	8	8	PBP-3 mutation (H370Y)
	1	8	8	
K. pneumoniae	0.06	0.5	8	
	0.12	0.5	4	
	0.25	2	8	
P. aeruginosa	025	2	8	PDC-30 mutation (4 AA deletion "TPMA" position 316-319)
	0.12	16	128	
	0.5	2	4	
S. maltophilia	0.06	0.25	4	
BAT arm**				
Ceftazidime/avibactam				
K. pneumoniae	0.25	16	64	
Tigecycline				
K. pneumoniae	1	>4	>4	
A. baumannii	2	>4	>4	
Colistin				
K. pneumoniae	≤0.5	>8	>16	
K. pneumoniae	≤0.5	8	>16	
A. baumannii	≤0.5	>8	>16	
A. baumannii	1	>8	>8	
E. coli	2	8	>4	

*Latest isolate before study drug initiation; **agents were selected based on local standard of care for CR infections, and MICs were confirmed by the central laboratory.

Table 2. MIC changes in APEKS-NP

Table 2. MIC changes in APEKS-NP				
Isolate	**MIC (μg/mL)**		**Fold change of MIC**	**Mutation identified the post-treatment isolates**
	Pre-treatment*	**Post-treatment**		
Cefiderocol arm				
E. aerogenes	0.06	0.5	8	
	0.06	0.5	8	
K. pneumoniae	≤0.03	0.12	≥4	
	0.06	0.25	4	
	0.25	1	4	
E. cloacae	1	4	4	ACT-17 mutation (A313P)
S. marcescens	0.06	0.25	4	
Meropenem arm				
K. pneumoniae	2	8	64	
P. aeruginosa	0.12	64	512	
	0.25	4	16	Opr-D truncation
	0.25	4	16	Opr-D truncation
C. freundii	≤0.03	0.12	4	
*Latest isolate before study drug initiation				

Conclusion. Among isolates with ≥4-fold MIC increase during CFDC treatment, actual CFDC MIC values remained relatively low for most isolates. Frequency of MIC increase in BAT or meropenem arms was similar to that of CFDC, but the magnitude was greater. Acquisition of contributory mechanism has not been identified except for the mutation in PBP 3 and some β-lactamases.

Disclosures. Miki Takemura, MSc, Shionogi & Co., Ltd. (Employee) Yoshinori Yamano, PhD, Shionogi & Co., Ltd. (Employee) Yuko Matsunaga, MD, Shionogi Inc. (Employee) Mari Ariyasu, BPharm, Shionogi & Co., Ltd. (Employee) Roger Echols, MD, Shionogi Inc. (Consultant) Tsutae Den Nagata, MD, Shionogi & Co., Ltd. (Employee)

1267. Comparative activity of omadacycline against extended-spectrum beta-lactamase positive and negative Escherichia coli and Klebsiella pneumoniae strains recovered from urine specimens

Tyler J. Stone, PharmD[1]; Abdullah Kilic, MD[1]; John Williamson, PharmD[2]; Elizabeth Palavecino, MD[2]; Elizabeth Palavecino, MD[2]; [1]Wake Forest Baptist Health, Winston-Salem, North Carolina; [2]Wake Forest Baptist Health System, Winston Salem, NC

Session: P-58. Novel Agents

Background. Omadacycline (OMC) is a novel tetracycline (TET) derivative antibiotic with activity against TET-resistant Enterobacterales. OMC is available in both oral and intravenous formulations and is has been studied as a treatment of uncomplicated urinary tract infection (UTI) and acute pyelonephritis. The purpose of this study was to evaluate OMC activity against extended-spectrum beta-lactamase (ESBL) positive and negative Enterobacterales strains recovered from urine specimens.

Methods. Urine samples from patients with suspected UTI were quantitatively plated onto blood agar and MacConkey agar plates in the microbiology lab of Wake Forest Baptist Medical Center. After overnight incubation, colonies were identified to the species level by MALDI-TOF system. Susceptibility testing was performed for isolates of *E. coli* and *K. pneumoniae*. OMC and TET susceptibility testing was performed by disk diffusion and gradient strip methodologies. Results were interpreted in accordance with the Clinical and Laboratory Standards Institute (CLSI) or Food and Drug Administration breakpoints. Isolates were tested in triplicate. ESBL screening and susceptibility testing to oral antibiotics commonly prescribed for UTI were performed by the MicroScan WalkAway System. Susceptibility rates and $MIC_{50}/_{90}$ were calculated and subsets of isolates were analyzed using descriptive statistics.

Results. A total of 204 isolates, including 102 *E. coli* and 102 *K. pneumoniae*, were tested. All but 1 isolate (99.5%) exhibited categorical agreement in results generated by the strip (Table 1) and disk (data not shown) methods and this was considered a minor error involving an intermediate result. OMC MIC_{90} for *E. coli* and *K. pneumoniae* were 6 μg/mL and >32 μg/mL, respectively. OMC displayed increased susceptibility rates compared to TET regardless of isolate species or ESBL positivity (Table 2).

Table 1. Omadacycline Minimum Inhibitory Concentrations (MICs, μg/mL)

	MIC_{50}	MIC_{90}	Min MIC	Max MIC	Modal MIC
All *E. coli* and *K. pneumoniae* (n=204)	4	16	0.25	>32	4
E. coli (n=102)	3	6	0.25	>32	4
ESBL positive (n=51)	4	12	0.25	>32	4
ESBL negative (n=51)	2	4	1	8	3
K. pneumoniae (n=102)	4	>32	1.5	>32	4
ESBL positive (n=51)	8	>32	1.5	>32	4
ESBL negative (n=51)	4	8	1.5	>32	4
All ESBLs (n=102)	4	>32	0.25	>32	4
Non-ESBLs (n=102)	3	4	1	>32	4

Table 2. Susceptibilities of Oral Antibiotics Used to Treat UTI (% S)

	OMC	TET	AMC	CIP	NIF	SXT
E. coli (n=93)	87.3	47.3	73.1	45.2	92.5	49.5
ESBL positive (n=49)	74.5	26.5	63.3	10.2	91.8	26.5
ESBL negative (n=44)	100	70.5	84.1	84.1	93.2	75.0
K. pneumoniae (n=88)	61.8	58.0	65.9	55.7	55.7	45.5
ESBL positive (n=43)	41.2	25.6	37.2	18.6	51.2	11.6
ESBL negative (n=45)	82.3	88.9	93.3	91.1	60.0	77.8

Conclusion: OMC exhibits promising antimicrobial activity against TET-resistant and ESBL-positive *E. coli* and *K. pneumoniae*. OMC displays superior activity to ESBL positive *E. coli* when compared to ESBL positive *K. pneumoniae*. These data support the development of OMC as a much needed option in the treatment of UTI caused by resistant Enterobacterales.

Disclosures. **Tyler J. Stone, PharmD**, **Paratek** (Research Grant or Support) **Abdullah Kilic, MD**, **Paratek** (Grant/Research Support) **John Williamson, PharmD**, **Paratek** (Research Grant or Support) **Elizabeth Palavecino, MD**, **Paratek** (Grant/Research Support)**Paratek** (Grant/Research Support)

1268. Dalbavancin for the Treatment of Infections due to Staphylococcus aureus

Amber C. Streifel, PharmD, BCPS[1]; Ellie Sukerman, MD[1]; Monica Sikka, MD[1]; Jina Makadia, MD[2]; James Lewis, PharmD[2]; Strnad Luke, MD[3]; [1]Oregon Health & Science University, Portland, Oregon; [2]Oregon Health and Science University, Portland, Oregon; [3]Oregon Health and Science University and Portland State University School of Public Health, Portland, Oregon

Session: P-58. Novel Agents

Background. Dalbavancin is a lipoglycopeptide antibiotic active against gram-positive organisms. Its extended half-life allows for weekly dosing that can last 4 to 6 weeks with 2 doses. Although approved for treating skin and soft tissue infections, use for more complicated infections is appealing, particularly when daily intravenous antibiotics are impractical. S aureus is the most common cause of complex infections for which dalbavancin is considered at our institution, so we sought to better understand its use.

Methods. We conducted a retrospective study to describe dalbavancin use at our institution for infections caused by Staphylococcus aureus. We identified all patients ≥18 years who received ≥1 dose of dalbavancin. Infectious disease faculty reviewed charts for clinical characteristics and outcomes of the infections.

Results. Fifty-two patients with S. aureus infections (60% MRSA) were treated with at least a partial course of dalbavancin. Twenty-seven (52%) had a history of IV drug use (IDU) and the most common infections were bone and joint infection in 51% and bacteremia in 40% (Table 1). The most common dosing regimen was 1500 mg x 1 in 55% or 1500 mg weekly x 2 in 25% (Table 2). The most common reasons for use of dalbavancin were history of IDU in 48% and lack of a safe home environment in 21%. Suppressive oral antibiotics for the primary infection were prescribed to 3 patients after completing dalbavancin (2 received for other indications). Clinical outcomes include 15% of patients lost to follow-up, readmission due to infection recurrence or dalbavancin adverse effects in 12%, and overall infection recurrence or relapse by day 90 in 31% (Table 3). There were no severe dalbavancin-related adverse drug events.

Table 1. Patient and Disease Characteristics

Table 1. Patient and Disease Characteristics

	n (%)
Demographics	
Age	Mean 45.5 years (STD 13.5)
Gender (Female)	15 (29%)
History of renal dysfunction	7 (13%)
History of hepatic dysfunction	14 (30%)
History of IVDU	27 (52%)
Indication	
Bone and joint infection (non-vertebral)	15 (29)
Vertebral osteomyelitis	11 (22)
Bacteremia	21 (40)
Skin and soft tissue infection	10(19)
Endocarditis	4 (8)
Vascular graft infection	2 (4)
Superinfected hepatic mass	1 (2)
Tenosynovitis	1 (2)
Endophthalmitis	1 (2)
Organism	
MRSA	31 (60)
MSSA	21 (40)
Diagnostic Imaging Performed in Workup	
TTE	29 (56)
TTE resulted as no vegetation or unexplained regurgitation	19 (66)
TEE	2 (4)
Spinal Imaging (CT scan or MRI)	17 (33)
Vascular imaging (venous duplex ultrasound)	13 (25)
Other cross-sectional imaging	18 (35)
Any additional imaging to assess for metastatic infection	5 (10)

Footnote: MRSA = methicillin resistant *S aureus* / MSSA = methicillin susceptible *S aureus* / IVDU = intravenous drug use / TTE = transthoracic echocardiography / TEE = transesophageal echocardiography / CT = computed tomography / MRI = magnetic resonance imaging; Indication: Multiple indications existed for some patients, so total % of study population > 100