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

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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.