Fig. 3

Figure 3: Isolation of *Staphylococcus* at Baseline and During, and After Dalbavancin Treatment (Evaluable Population)			
	Baseline	**Dalbavancin Treatment period**	**60 Days After End of IV Dalbavancin Treatment**
Osteomyelitis			
All patients (n=78)			
Specimen collected, n (%)	35 (44.9)	14 (17.9)	13 (16.7)
Isolates grown from the specimen?	29 (82.9)	8 (57.1)	7 (53.8)
Staphylococcus	20 (69.0)	6 (75.0)	2 (28.6)
Resistant to oxacillin	11/18 tested (61.1)	0 /4 tested (0.0)	1/1 tested (100.0)
Osteomyelitis of the Foot (n=51)			
Specimen collected, n (%)	24 (47.1)	10 (19.6)	9 (17.6)
Any isolates grown from the specimen?	21 (87.5)	6 (60.0)	5 (55.6)
Staphylococcus	14 (66.7)	5 (83.3)	1 (20.0)
Resistant to oxacillin	8 /13 tested (61.5)	0/3 tested (0.0)	1 (100.0)
Joint Infection (n=32)			
Any specimen collected, n (%)	19 (59.4)	3 (9.4)	2 (6.3)
Any isolates grown from the specimen?	15 (78.9)	2 (66.7)	2 (100.0)
Staphylococcus	15 (100.0)	2 (100.0)	2 (100.0)
Resistant to oxacillin	5/14 tested (35.7)	0/1 tested (50.0)	1/2 tested (50.0)

Conclusion. In this real-world study in patients with Staphylococcal osteomyelitis and joint infection, DAL resulted in high rates of clinical and microbiological success.

Disclosures. Jennifer McGregor, RPh, AbbVie (Employee) Anathakrishnan Ramani, MD, FACP, AAHIVS, CIC, Allergan (prior to its acquisition by AbbVie) (Speaker's Bureau) John Lock, PharmD, BCPS, AQ-ID, AbbVie (Employee) Pedro Gonzalez, MD, MT, AbbVie (Employee)

1248. Efficacy and Safety of Oral Ibrexafungerp in 41 Patients with Refractory Fungal Diseases, Interim Analysis of a Phase 3 Open-label Study (FURI)

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Session: P-58. Novel Agents

Background. *Candida* infections resistant to currently available antifungals are an emerging global threat. Ibrexafungerp is an investigational broad-spectrum glucan synthase inhibitor antifungal with activity against *Candida* and *Aspergillus* species, including azole- and echinocandin-resistant strains. A Phase 3 open-label, single-arm study of oral ibrexafungerp (FURI) (Clinicaltrials.gov NCT03059992) is ongoing for the treatment of patients (≥18 years) with fungal diseases who are intolerant of or refractory to standard antifungal therapies.

Methods. An independent Data Review Committee (DRC) provided an assessment of treatment response for 41 patients. Patients were enrolled in 22 centers from 6 countries. Patients were eligible for enrollment if they had proven or probable, invasive or severe mucocutaneous candidiasis and documented evidence of failure of, intolerance to, or toxicity related to a currently approved standard-of-care antifungal treatment or could not receive approved oral antifungal options (e.g., susceptibility of the organism) and a continued IV antifungal therapy was undesirable or unfeasible.

Results. The 41 patients assessed had the following infection types: intra-abdominal abscesses, oropharyngeal candidiasis, esophageal candidiasis, candidemia, and others. The DRC adjudicated 23 patients (56%) as achieving complete or partial response, 11 patients (27%) maintaining stable disease, 6 patients (15%) with progression of disease and one case was considered as indeterminate. The efficacy of oral ibrexafungerp by pathogen is shown in Table 1. Ibrexafungerp was well-tolerated with the most common treatment-related adverse events being of gastrointestinal origin. No deaths due to progression of fungal disease were reported.

Table 1: Ibrexafungerp Outcomes by Pathogen

Pathogen	Complete or Partial Response	Stable disease	Progression of Disease
C. glabrata	9	5	3
C. albicans	5	2	
C. krusei	2	3	
C. parapsilosis	3		
C. glabrata / C. albicans	2		2
C. krusei / C. albicans	1		
C. tropicalis / C. albicans		1	
C. glabrata / C. dubliniensis			1

One patient outcome indeterminate, One patient organism not identified

Conclusion: Preliminary analysis of these 41 cases indicate that oral ibrexafungerp provides a favorable therapeutic response in the majority of patients with difficult to treat *Candida* spp. infections, including those caused by *non-albicans Candida* species.

Disclosures. **Barbara D. 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1249. Genetic Evidence That Gepotidacin Shows Well-balanced Dual Targeting against DNA Gyrase And Topoisomerase IV in Neisseria gonorrhoeae

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Session: P-58. Novel Agents

Background. Gepotidacin (GEP) is a novel triazaacenaphthylene bacterial type II topoisomerase inhibitor targeting both bacterial DNA gyrase and topoisomerase IV by a different mechanism from fluoroquinolone antibiotics. Although in vitro frequency of resistance to GEP in *Neisseria gonorrhoeae* (NG) is low, during a phase 2 trial, clinical resistance to gepotidacin in NG emerged in a subset of fluoroquinolone-resistant NG isolates that contained a pre-existing ParC D86N mutation by introduction of a new GyrA A92T mutation. The objective of this study was to evaluate the role of GyrA A92T & Parc D86N mutations in resistance to GEP.

Methods. We utilized the high frequency of natural transformation to introduce GyrA A92T and ParC D86N mutations, individually and in combination, into NG isolates either with GyrA S91F D95G mutations or with wild type (WT) GyrA by selection on ciprofloxacin (CIP) or GEP to generate isogenic strains for susceptibility evaluation.

Results. Results are summarized in enclosed table. Overall, GyrA A92T and ParC D86N mutations alone did not confer a significant (>4-fold) increase in GEP MIC; whereas together they gave >16-fold increases in GEP MIC. Importantly, quinolone target mutations (GyrA S91F D95G and ParC D86N) together showed no significant effect on the GEP MIC; while they gave >1000-fold increase in CIP MIC. As expected, GyrA A92T and ParC D86N mutations alone or together in WT GyrA background had no significant effect on CIP susceptibility.

Susceptibility of isogenic NG strains to gepotidacin and ciprofloxacin

	Mutation in			MIC (ug/ml)/fold change from wt	
NG strain	GyrA	ParC	*mtrR*$_p$	GEP	CIP
FA1090	wt	wt	wt	0.063	0.004
FA1090-1	S91F D95G	wt	wt	0.063/1	0.5/128
FA1090-3	S91F A92T D95G	wt	wt	0.125/2	0.5/128
FA1090-2	S91F D95G	D86N	wt	0.125/2	4/1024
FA1090-4	S91F A92T D95G	D86N	wt	8/128	4/1024
FA1090E	wt	wt	*mtrR*$_{-79}$	0.25	0.004
FA1090E-1	A92T	wt	*mtrR*$_{-79}$	0.5/2	0.002/0.5
FA1090E-2	wt	D86N	*mtrR*$_{-79}$	0.25/1	0.004/1
FA1090E-3	A92T	D86N	*mtrR*$_{-79}$	4/16	0.002/0.5

Conclusion. Our results indicated that unlike fluoroquinolones that primarily target DNA gyrase in NG, there is no obvious primary target for GEP, supporting well-balanced dual targeting of DNA gyrase and topoisomerase IV by GEP in NG. Though, the pre-existing ParC D86N mutation is a potential risk marker for clinical resistance development, as this mutation compromises dual targeting of GEP, our studies provide mechanistic insight for appropriate clinical dose selection to potentially suppress further resistance development in this subset of clinical isolates.

Disclosures. Pan Chan, PhD, GlaxoSmithKline (Employee, Shareholder) Karen Ingraham, MS, GlaxoSmithKline (Employee, Shareholder) Sharon Min, MS, GlaxoSmithKline (Employee, Shareholder) Nicole Scangarella-Oman, MS, GlaxoSmithKline plc. (Employee, Shareholder) Steve Rittenhouse, PhD, GlaxoSmithKline (Employee, Shareholder) Jianzhong Huang, PhD, GlaxoSmithKline (Employee, Shareholder)

1250. Novel Boronic Acid Transition State Analogs (BATSI) with in vitro inhibitory activity against class A, B and C β-lactamases

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Session: P-58. Novel Agents

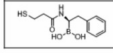
Background. Catalytic mechanisms of serine β-lactamases (SBL; classes A, C and D) and metallo-β-lactamases (MBLs) have directed divergent strategies towards inhibitor design. SBL inhibitors act as high affinity substrates that -as in BATSIs- form a reversible, dative covalent bond with the conserved active site Ser. MBL inhibitors bind the active-site Zn^{2+} ions and displace the nucleophilic OH^-. Herein, we explore the efficacy of a series of BATSI compounds with a free-thiol group at inhibiting both SBL and MBL.

Methods. Exploratory compounds were synthesized using stereoselective homologation of (+) pinandiol boronates to introduce the amino group on the boron-bearing carbon atom, which was subsequently acylated with mercaptopropanoic acid. Representative SBL (KPC-2, ADC-7, PDC-3 and OXA-23) and MBL (IMP-1, NDM-1 and VIM-2) were purified and used for the kinetic characterization of the BATSIs. *In vitro* activity was evaluated by a modified time-kill curve assay, using SBL and MBL-producing strains.

Results. Kinetic assays revealed that IC_{50} values ranged from 1.3 μM to >100 μM for this series. The best compound, s08033, demonstrated inhibitory activity against KPC-2, VIM-2, ADC-7 and PDC-3, with IC50 in the low μM range. Reduction of at least 1.5 log_{10}-fold of viable cell counts upon exposure to sub-lethal concentrations of antibiotics (AB) + s08033, compared to the cells exposed to AB alone, demonstrated the microbiological activity of this novel compound against SBL- and MBL-producing *E. coli* (Table 1).

Table 1

Table 1. IC_{50} values and *in vitro* activity results for s08033 against selected SBLs and MBLs.

s08033	VIM-2	KPC-2	ADC-7	PDC-3
	IC_{50} = 2.8±0.3 μM log_{10} diff = 4	IC_{50} = 16±2 μM log_{10} diff = 5	IC_{50} = 13 ±2 μM log_{10} diff = 1.5	IC_{50} = 4.4±0.4 μM log_{10} diff = 4

Conclusion. Addition of a free-thiol group to the BATSI scaffold increases the range of these compounds resulting in a broad-spectrum inhibitor toward clinically important carbapenemases and cephalosporinases.

Disclosures. Robert A. Bonomo, MD, Entasis, Merck, Venatorx (Research Grant or Support)

1251. Prevention of Pneumocystis Pneumonia by Ibrexafungerp in a Murine Prophylaxis Model

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Session: P-58. Novel Agents

Background. *Pneumocystis* pneumonia (PCP) is an opportunistic fungal infection that affects immunocompromised patients. Ibrexafungerp (IBX) is an oral and intravenous antifungal from a novel class of glucan synthase inhibitors, triterpenoids, and has shown activity against *Candida*, *Aspergillus*, and PCP in a murine therapy model. We evaluated the ability of IBX to prevent PCP in a prophylaxis model of murine PCP.

Methods. **Experiment 1:** Balb/c mice (10 mice/group) were infected by intranasal inoculation with *Pneumocystis murina*, immune-suppressed with dexamethasone in acidified drinking water and treated with 30-, 15- and 7.5 mg/kg, IBX/BID. Control groups treatment included TMP-SMX (50/250 mg/kg QD) and vehicle. After 6 weeks, mice were sacrificed, and prevention was determined by organism burdens (asci and total nuclei). **Experiment 2**: Balb/c mice were immune-suppressed and infected as in Exp. 1. Treatment groups included: 1) 30 mg/kg BID x 6wk; 2) 30 mg/kg/BID x 6wk followed by cessation of treatment with IBX but with immune-suppression for 3 additional weeks; 3) 15 mg/kg BID 1 week prior and 6 wks after infection and immune suppression; 4) 15mg/kg BID for 8 wks; 5) 15 mg/kg BID for 6 wks then IBX was discontinued but with immune suppression; 6) untreated, vehicle control.

Results. **Experiment 1:** No *P. murina* nuclei or asci were observed after 6 weeks of treatment at a dose of 30 mg/kg/BID in the prophylaxis mouse model of PCP, similar to positive control, TMP/SMX. Some nuclei and asci were observed in the lower dose IBX groups. **Experiment 2:** To investigate whether any *P. murina* remained after different regimens of prophylaxis, treatment of IBX was withdrawn at both doses for an additional 3 wks of immune suppression to provoke the growth of any remaining fungi. Group 1 showed reduction in total nuclei and asci to undetectable. Group 2 did not result in any recrudescence of infection. Group 3 and 4 showed similar reduction in organism burden. Group 5 was similar to untreated control.

Conclusion. These results demonstrate that 30 mg/kg BID IBX prevented PCP in a murine model. We suggest that IBX could be a viable option for preventing PCP in immunocompromised patients.

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1252. In Vitro Activity of Cefiderocol Against Metallo-β-Lactamase-Producing Gram-Negative Bacteria Collected in North America and Europe Between 2014 and 2017: SIDERO-WT-2014–2016 Studies

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Session: P-58. Novel Agents

Background. Metallo-β-lactamases (MBLs; eg, NDM, VIM, and IMP) can inactivate most commonly-used β-lactam antibiotics, including carbapenems. Infections caused by MBL producers are difficult to treat due to their resistance to many antibiotics. Cefiderocol (CFDC) is a siderophore cephalosporin antibiotic approved in the USA in 2019, with potent activity against carbapenem-resistant Gram-negative bacteria (GNB), including both serine- and metallo-carbapenemase positive strains. We evaluated the *in vitro* activity of CFDC and comparator agents against MBL-producing strains of GNB from North America and Europe in 3 years' of consecutive surveillance studies (SIDERO-WT-2014–2016).

Methods. Susceptibility testing for CFDC, ceftazidime-avibactam (CZA), ceftolozane-tazobactam (C/T), meropenem (MEM), cefepime (FEP), ciprofloxacin (CIP), and colistin (CST) was performed by broth microdilution according to CLSI guidance. CFDC was tested in iron-depleted medium. A total of 275 MBL-producing strains, consisting of 120 Enterobacterales (45 NDM; 75 VIM), 5 NDM-producing *Acinetobacter baumannii*, and 150 *Pseudomonas aeruginosa* (134 VIM; 16 IMP), identified among