Disclosures. M. R. Jacobs: Achaogen: Investigator, Research grant. Shionogi: Investigator, Research grant. S. S. Richter: bioMerieux: Grant Investigator, Research grant. BD Diagnostics: Grant Investigator, Research grant. Roche: Grant Investigator, Research grant. Hologic: Grant Investigator, Research grant. Diasorin: Grant Investigator, Research grant. BD Diagnostics: Grant Investigator, Research grant. Research grant. Roche: Investigator, Research grant. Social: Consultant fee. Astellas: Scientific Advisor, Consulting fee. Allergan: Scientific Advisor, Consulting fee. Astellas: Scientific Advisor, Consulting fee. Neumedicine: Consultant, Consulting fee. T2 Biosystems: Scientific Advisor, Consulting fee. Roche: Scientific Advisor, Consulting fee.

1352. A Computational Approach for Exploring the Binding Mechanism of Chebulenic Acid on Herpes Simplex Virus-2 and Its Implication on Chikungunya and Dengue
Najus Thomas, MPhil; Sandeep Kumar, MSc; Vikas Kumar, MSc and Suman Tapryal, Ph.D; Biotechnology, Central University of Rajasthan, Ajmer, India

Session: 144. Novel Agents
Friday, October 5, 2018: 12:30 PM

Background. Chebulenic acid (CA), a natural compound isolated from the tree Terminalia chebula, recently was found to have shown antiviral activity against Herpes simplex virus-2 (HSV-2). The study showed inhibition activity of CA, preventing the attachment of HSV-2 on the host cells. This activity was speculated to be due to an interaction between CA and viral surface glycoproteins, triggering alterations in its function or making virus particles inert and preventing their attachment to host cells. However, the mechanism of this inhibition was not established. The current study was designed not only to help gain insights of the mechanism of action of CA on HSV-2, but also to computationally check its binding affinity on other enveloped arboviruses, i.e., Chikungunya virus (ChikV) and Dengue (DenvV).

Methods. The viral surface glycoproteins of HSV-2, ChikV, and DenV were subjected to molecular docking with CA using the software, AutoDock Vina. Protein–protein docking was performed with ChUsPro online server to elucidate the specific site and residues involved in the binding between viral protein and human host receptors. Due to unavailability of crystal structure of Prohibitin, a human receptor for ChikV, structural modeling was performed with i-Tasser server.

Results. The conformations obtained after docking showed good hydrogen bond interactions with the docked energy of -9.3, -3.1, and -8.8 kcal/mol at HSV-2, ChikV, and DenV, respectively. In all three viruses, CA was found to bind specifically at the site directly involved in host attachment, suggesting a possible mechanism of action by which CA inhibits the viral attachment that is consistent with the result obtained from the binding experiment on HSV-2. Hence, the natural molecule Chebulenic acid has the potential to inhibit the host attachment step of HSV-2, ChikV, and DenV by directly binding to their viral glycoproteins.

Conclusion. Chebulenic acid shows a good propensity as an antiviral agent, capable of acting against multiple enveloped viruses. Additionally, a more potent and specific drug can be designed on the template of CA by process of molecular modification.

Disclosures. N. Thomas, Department of Science and Technology: Government of India funding agency, Research grant. S. Kumar, University Grants Commission: Government of India funding agency, Research grant. V. Kumar, University Grants Commission: Government of India funding agency, Research grant. S. Tapryal, Department of Science and Technology: Government of India funding agency, Research grant.

1353. In Vitro Activity of Lefamulin (LEF) Against Bacterial Pathogens Commonly Causing Community-Acquired Bacterial Pneumonia (CABP): 2016 SENTRY Data From the United States
Sussan Paukner, PhD; Robert K. Flamm, PhD2; Steven P. Gelone, PharmD and Helio S. Sader, MD, PhD1; Nabriva Therapeutics GmbH, Vienna, Austria, 1MJ Laboratories, Inc., North Liberty, Iowa, 2Nabriva Therapeutics US, Inc., King of Prussia, Pennsylvania, 1MJ Laboratories, North Liberty, Iowa

Session: 144. Novel Agents
Friday, October 5, 2018: 12:30 PM

Background. LEF, the first pleuromutilin antibiotic for IV and oral use in humans, is in Phase 3 clinical trials for the treatment of CABP in adults. In the first of these studies, LEF demonstrated non-clinical trough (trough), with modestly lower total and peak exposure when administered under fed conditions compared to the fasted state (fed/fasted ratios of 78.09% for C max; 14,183.2 vs. 18,479.4 73.05% for C trough, 1,519.4 vs. 2,085.2 and 91.53% for C AUC, 1,571.5 vs. 1,218.5). The C max was well-tolerated by the healthy subjects participating in this study.

Conclusion. The results demonstrate a promising clinical utility for SUBA-Itraconazole in practice. Unlike the conventional capsule formulation which requires a high fat meal for absorption, or the oral solution formulation which requires a fasted state, SUBA-Itraconazole achieved the therapeutic steady state in both fasted and fed states. The similar trough level, however higher peak with fasted state, likely represents a more gradual absorption of drug in the fed state. The slightly higher bioavailability in a fasted state, without gastrointestinal intolerability, is particularly promising for the clinical use of SUBA-Itraconazole in patients unable to have a high fat content meal due to chemotherapy or post-surgery such as hematology patients and transplant recipients.

Figure 1. Mean pre-dose plasma itraconazole concentrations.

[Table of MIC50 of Lefamulin and Comparisons]

Organism(s) | Lefamulin | Linezolid | Avibactam/IMI | Comparisons |
--- | --- | --- | --- | --- |
S. aureus | 0.05/0.12 | 0.06/0.12 | 0.15/0.3 | A2 > A1 > A3 |
S. pneumoniae | 0.05/0.12 | 0.06/0.12 | 0.32/0.64 | A2 > A1 > A3 |
H. influenzae | 0.03/0.06 | 0.03/0.06 | 0.06/0.12 | A2 > A1 > A3 |
P. mirabilis | 0.08/0.16 | 0.03/0.06 | 0.03/0.06 | A2 > A1 > A3 |
K. pneumoniae | 0.08/0.16 | 0.03/0.06 | 0.03/0.06 | A2 > A1 > A3 |
Enterococcus | 0.25/0.5 | 0.25/0.5 | 0.25/0.5 | A2 > A1 > A3 |
M. chusae | 0.5/1 | 0.5/1 | 0.5/1 | A2 = A1 > A3 |
A. baumannii | 4 | 4 | 4 | A2 > A1 > A3 |
A. Fuji (ATCC) | 0.08/0.16 | 0.08/0.16 | 0.08/0.16 | A2 > A1 > A3 |
A. Fuji (ATCC) | 0.08/0.16 | 0.08/0.16 | 0.08/0.16 | A2 > A1 > A3 |

Disclosures. S. Paukner, Nabriva: Employee and Shareholder, Salary. R. K. Flamm, Nabriva: Research Contractor, Research grant. S. P. Gelone, Nabriva: Therapeutics: Employee, Equity, Shareholder and Salary. Achaogen: Shareholder, Equity, Shareholder. H. S. Sader, Nabriva: Therapeutics: Research Contractor, Research support.

1354. Novel Formulation SUBA-Itraconazole in Fed and Fasted Healthy Volunteers: Expanding the Clinical Utility of the Established Mold Active Agent
Julian Lindsay, BPharm(Hons)1 and Stuart Mudge, PhD1; MClinPharm, Royal North Shore Hospital, Sydney, Australia, 2Mayne Pharma, Melbourne, Australia

Session: 144. Novel Agents
Friday, October 5, 2018: 12:30 PM

Background. SUBA-Itraconazole has been established as an effective mold active agent, however, wide interpatient variability in bioavailability and poor gastrointestinal tolerability have made using the agent challenging. A novel formulation, SUBA-Itraconazole (SUBPerBioAvailable) has been developed by Mayne Pharma to alleviate these negative properties.

Methods. An open-label, randomized, cross-over study of SUBA-Itraconazole capsules 65 mg (2 × 65 mg BID) in healthy adults under fasting and fed conditions was assessed for steady-state levels. Subjects (n = 20) were administered two capsules of SUBA-Itraconazole twice daily for 14 days and once on the morning of Day 15, either on an empty stomach or with a meal. Safety was monitored by vital signs measurements, electrocardiogram measurements, clinical safety laboratory tests (liver and kidney function tests), and physical examination.

Results. Overall, SUBA-Itraconazole demonstrated similar concentrations at the end of the dosing interval (trough), with modestly lower total and peak exposure when administered under fed conditions compared to the fasted state (fed/fasted ratios of 78.09% for AUC, 14,183.2 vs. 18,479.4 73.05% for C max, 1,519.4 vs. 2,085.2 and 91.53% for C AUC, 1,571.5 vs. 1,218.5). See Figure 1 and 2. The administration of SUBA-Itraconazole 65 mg capsules was well-tolerated by the healthy subjects participating in this study.

Conclusion. The results demonstrate a promising clinical utility for SUBA-Itraconazole in practice. Unlike the conventional capsule formulation which requires a high fat meal for absorption, or the oral solution formulation which requires a fasted administration, SUBA-Itraconazole reached a therapeutic steady state in both fasted and fed states. The similar trough level, however higher peak with fasted state, likely represents a more gradual absorption of drug in the fed state. The slightly higher bioavailability in a fasted state, without gastrointestinal intolerability, is particularly promising for the clinical use of SUBA-Itraconazole in patients unable to have a high fat content meal due to chemotherapy or post-surgery such as hematology patients and transplant recipients.
Figure 2: Mean plasma itraconazole concentration–time profile (day 15).

Disclosures. J. Lindsay, Mayne Pharma: Consultant, Consulting fee. S. Mudge, Mayne Pharma: Employee, Salary.

1355. Global Activity of Imipenem–Relebactam and Comparators Against Clinical Gram-Negative Pathogens – SMART 2017

Shybly Lob, PhD1; Krystyna Kazmierczak, PhD1; Daryl Hoban, PhD2; Meredith Hackel, PhD1; Katherine Young, MS1; Mary Moty1, PhD3 and Dan Sahm, PhD1; 1IHMA, Inc., Schaumburg, Illinois, 2Merk, Inc., Menlo Park, Pennsylvania, and 3International Health Management Associates, Inc., Schaumburg, Illinois.

Session: 144. Novel Agents
Friday, October 5, 2018: 12:30 PM

Background. Relebactam (REL), formerly MK-7655, is a β-lactamase inhibitor of class A and C β-lactamases that is in development in combination with imipenem (IMI). In this study, we evaluated the activity of IMI/REL against recent clinical isolates of Gram-negative bacteria (GNB) collected globally as part of the SMART surveillance program.

Methods. In 2017, 188 hospitals in 54 countries each collected up to 100 consecutive Gram-negative aerobic or facultatively anaerobic pathogens from lower respiratory tract infections, 75 from intra-abdominal infections, and 75 from urinary tract infections. MICs were determined for 4,139 GNB, including 30,846 Enterobacteriaceae and 6,933 P. aeruginosa isolates, using CLSI broth microdilution and interpreted with CLSI breakpoint; for comparison purposes, IMI susceptible breakpoints were applied to IMI/REL.

Results. Susceptibilities to IMI/REL and comparators of the 10 most commonly found Enterobacteriaceae species and P. aeruginosa are shown below.

Figure 1.

Figure 2.

Figure 2: Change from Baseline in SF-36 v2 Parameters

OMADACYCLINE vs. LINEZOLID

OMADACYCLINE

LINEZOLID

Disclosures. E. Tsanis, Paratek Pharmaceuticals: Employee, Salary. M. Curran, Paratek Pharmaceuticals: Employee, Salary. P. McGovern, Paratek Pharmaceuticals: Employee, Salary. J. Hinahara, Paratek Pharmaceuticals: Consultant, Consulting fee. T. Goss, Paratek Pharmaceuticals: Consultant, Consulting fee.

1357. A Combination of Itraconazole and Amiodarone Is Highly Effective Against Trypanosoma cruzi Infection of Human Stem Cell-Derived Cardiomyocytes

Gabrielle Saas, PhD1; Roy Madigan, DVM2; Adriana Bozzi, PhD3;4; Nazih Sayed, MD, PhD3;4; Joseph Wu, MD4 and David Steven, MD5;6; 1California Institute for Medical Research, San Jose, California, 2Animal Hospital of Smithson Valley, 3Animal Medical Center, New York, New York, 4Stanford University School of Medicine, Stanford, California, and 5Veterans Affairs Palo Alto Health Care System, Menlo Park, California.

Session: 144. Novel Agents
Friday, October 5, 2018: 12:30 PM

Background. The appearance of multidrug-resistant Gram-positive bacteria is a major challenge in clinical care. Omadacycline is the first aminomethylcycline antibiotic (semisynthetic compounds related to tetracyclines) in late-stage clinical development for acute bacterial skin and skin structure infections (ABSSSI), and demonstrates potent in vitro activity against many pathogens.

Methods. Seven hundred thirty-five patients were enrolled in the OASIS-2 randomized controlled trial comparing omadacycline and linezolid for the treatment of adult subjects with ABSSSI known or suspected to be due to a Gram-positive pathogen, with 368 and 367 enrolled in each group, respectively. Subjects completed the 36-Item Short Form Health Survey Version 2 (SF-36v2), a validated questionnaire on physical and mental health, at both screening and post-treatment evaluation. Results of the SF-36v2 were analyzed in accordance with established norm-based standards for the survey (Ware 2000) for the intention-to-treat population.

Results. Subjects who received omadacycline experienced a 3.25 point mean improvement in overall physical health (P < 0.001, Figure 1) and reported significant improvements across all but one component parameter of overall physical and mental health, including physical functioning, bodily pain, role physical, vitality, role emotional, mental health, and social functioning (Figure 2). In contrast, while overall physical health improved for subjects who received linezolid, the improvement in vitality, role emotional, mental health, and general health was not significant (Figure 2). Although omadacycline achieved greater increase from baseline than linezolid across all domains analyzed, the difference in scores was not statistically significant at the P < 0.05 level (Figure 1).

Conclusion. Omadacycline provides significant improvement in the physical component of quality of life over baseline for adult subjects with ABSSSI known or suspected to be due to a Gram-positive pathogen. Although the OASIS-2 trial was neither designed nor powered to measure differences in quality of life following treatment, trends identified in this analysis merit further investigation.

References
1. Ware JE. SF-36 Health Survey Update. SPINE 2000; 25(24); 3130–3139.