1963. Combined Microbiological Response Rates From Two Phase 3 Trials Demonstrating the Activity of Eravacycline in the Treatment of Complicated Intra-abdominal Infections: A Pooled Analysis of IGNITE1 and IGNITE4

Joseph Newman, PhD; Sergey Imaizumi, MS; Corey Frye, MS and Larry Tsai, MD; Tetraphase Pharmaceuticals, Watertown, Massachusetts

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Background. IGNITE1 and IGNITE4 were randomized, double-blind, double-dummy, multicenter trials which compared the efficacy and safety of eravacycline (ERV) with a carbapenem in subjects with complicated intra-abdominal infections (cIAIs). The primary objective of this analysis was to compare the microbiological response at the test-of-cure (TOC) visit for subjects in the two treatment groups.

Methods. Appropriate aerobic and anaerobic specimens for culture at the time of the initial procedure were collected from the site of infection and directly inoculated into transport media. Blood and intra-abdominal specimens were cultured, and species identified according to local laboratory practice. Pure cultures of isolates were sent to a reference laboratory for susceptibility analysis to ERV and comparators. Favorable microbiological response rates at the TOC visit were determined for each baseline pathogen isolated from blood and/or intra- or extra-abdominal specimens in the micro-ITP population.

Results. For subjects with infections caused by Enterobacteriaceae, the overall favorable microbiological response rates for ERV-treated subjects were 86.3% and 91.8% for IGNITE1 and IGNITE4, respectively. The favorable microbiological response rates among pooled ERV-treated subjects are shown in the Table.

Table. Microbiological Response at TOC in BSIs by Pathogen, Resistance Phenotype, and Genotype

| Pathogen or Genotype Category | Randomized Cohort | Observational Cohort |
|------------------------------|-------------------|----------------------|
|                               | PLZ (N = 14)      | CST (N = 15)         | Difference PLZ Minus CST (% G) |
|                               |                   |                      |                               |
| Enterobacteriaceae            |                   |                      |                               |
| E. coli                      | 223/283 (80.3)    | 190/210 (89.8)       | 30 (11.2 to 65.6)             |
| E. cloacae                    | 162/187 (86.5)    | 145/164 (88.6)       | 27 (11.7 to 64.7)             |
| Enterobacter aerogenes        | 1/1 (100)         | 0                    | -                              |
| Enterococcus faecalis         | 1/1 (100)         | 0                    | -                              |
| A. baumannii                  | 13/100 (13)       | 7/84 (8.8)           | 0                              |
| Streptococcus viridans group  |                   |                      |                               |
| E. faecalis                  | 45/54 (83.3)      | 45/54 (83.3)         | 0                              |
| E. faecium                   | 39/45 (86.7)      | 39/45 (86.7)         | 0                              |
| K. pneumoniae                | 188/209 (89.4)    | 187/209 (89.4)       | 0                              |
| S. aureus                    | 24/44 (54.5)      | 44/44 (100)          | 0                              |
| F. necrophorum               | 4/8 (50)          | 4/8 (50)             | 0                              |
| F. meningitidis              | 3/13 (23)         | 3/13 (23)            | 0                              |
| C. albicans                  | 42/42 (100)       | 42/42 (100)          | 0                              |
| C. jejuni                    | 34/55 (61.8)      | 43/65 (66.2)         | 9 (23.4 to 49.0)               |
| N. gonorrhoeae               | 1/1 (100)         | 0                    | -                              |
| N. meningitidis              | 2/3 (66.6)        | 0                    | -                              |

Conclusion. In IGNITE1 and IGNITE4 studies, high favorable microbiological responses were observed for ERV. More than 88% of five Enterobacteriaceae spp. and B. fragilis, the most common bacteria associated with intra-abdominal infections, were eradicated by ERV. Comparable eradication rates were observed following eravacycline and meropenem therapy, further establishing that ERV was at least as effective as carbapenem treatments. These data support in vitro observations that ERV has broad-spectrum activity against common isolates found in intra-abdominal infections.

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1964. Microbiological Outcomes With Plazomicin (PLZ) vs. Colistin (CST) in Patients With Bloodstream Infections (BSI) Caused by Carbapenem-Resistant Enterobacteriaceae (CRE) in the CARE Study

Alisa W. Serio, PhD,1 Alex Smith, MS,1 Kevin M. Krause, MBA,1 Irene Galani, PhD,1 Ana Cristina Gales, MD, PhD,2 Adrian Jubb, MBChB, PhD, FRCPath3 and Lynn E. Connolly, MD, PhD,4 Achaogen, Inc., South San Francisco, California, and Stanford University, Stanford, California

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Abstract background. Plazomicin (PLZ) is a new oral monobactam that has been approved by the US Food and Drug Administration for the treatment of complicated urinary tract infections. In the CARE study, PLZ was associated with improvement in 28-day all-cause mortality vs. CST in patients with CRE BSI. We report the microbiological outcomes in the CARE study pathogen by key resistance mechanism.

Methods. CARE was a multinational, open-label trial that enrolled BSI patients with documented or presumed CRE into two cohorts. Patients in the randomized cohort received PLZ (15 mg/kg/day) plus adjunctive tigecycline or meropenem. Patients in the observational cohort received PLZ plus investigator’s choice of adjunctive treatment. Duration 7-14 days. Isolate identification and susceptibility testing were conducted by a central laboratory. Whole-genome sequencing was used to identify AME and carbapenemase genes. Microbiological outcomes were assessed in patients with confirmed CRE who received ≥2 doses of study drug (mMITT population).

Results. Of 45 BSI patients enrolled, 43 had confirmed CRE (mMITT, including Klebsiella pneumoniae (n = 42) and Enterobacter aerogenes (n = 1). Against CRE, PLZ MICs ranged from 0.12 to ≥256 µg/mL. 25/28 (89.3%) isolates from PLZ-treated patients had a PLZ MIC ≤4 µg/mL while 3 had a PLZ MIC ≥256 µg/mL and a confirmed 165 ribosomal methyltransferase gene. CST MICs ranged from 0.25 to >128 µg/mL; 6/16 (37.5%) isolates from CST-treated patients had an MIC >2 µg/mL. There were 47 distinct Enterobacteriaceae pathogens isolated from 43 patients, and of these, AME genes were detected in 43/47 (91.5%), most commonly ace (6):B (n = 29). Carbapenemase genes were detected in 45/47 (95.7%) isolates, most commonly blaKPC (n = 33). PLZ demonstrated higher microbiological eradication rates than CST against CRE, including AME- and carbapenemase-producing isolates (table).

Conclusion. The results provide evidence of the efficacy of PLZ-based therapy for patients with BSI due to MDR Enterobacteriaceae, including AME- and carbapenemase-producing organisms.

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1965. Safety and Efficacy of Gilead’s GSK1269904 in Patients With Chronic Hepatitis C Virus Genotypes 1–6 and Human Immunodeficiency Virus-1 Co-Infection: An Integrated Analysis of Two Phase 3 Clinical Trials

Jürgen K Rockstroh, MD; Sanjay R Baghadi, MD; Chloe Orkin, MBChB; Ruth Soto-Malave, MD;1 Karine Lacombe, MD, PhD;2 Zhenzhun Zhang, PhD;2 Stanley Wang, MD, PhD;2 Federico Mena, MD2 and Roger Trinh, MD, MPH;2 Universitätsklinikum Bonn, Bonn, Germany, “Royal Free London Foundation Trust, London, UK, “The Royal London Hospital, London, UK, “Innovative Care PS, S.C., Bayamon, Puerto Rico, “InsERM-U9116, Université Pierre et Marie Curie, Hôpital Saint-Antoine, Paris, France, “AbbVie Inc., North Chicago, Illinois

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Background. People co-infected with hepatitis C virus (HCV) and human immunodeficiency may experience virus (HIV-1) may be treated for HCV without special considerations apart from drug interactions with antiretroviral therapies (ART). The once-daily, all-oral, ribavirin-free, pan-genotypic combination of glecaprevir (identifized by AbbVie and Enanta) and pibrentasvir has shown high sustained virologic response at post-treatment Week 12 (SVR12) in HCV mono-infected patients. We evaluated the safety/efficacy of glecaprevir/pibrentasvir in patients co-infected with HCV/HIV-1.

Methods. Data were pooled from two Phase 3 trials for treatment-naïve and -experienced patients co-infected with HCV genotypes (GT) 1–6/HIV-1 without cirrhosis or with compensated cirrhosis who received glecaprevir/pibrentasvir for 8 or 12
weeks. Virologic response, adverse events (AEs), and laboratory abnormalities were evaluated.

Results. Across the two trials, 152 patients without cirrhosis and 16 with compensated cirrhosis received genclovir/pirenaltavir for 8 and 12 weeks, respectively. Baseline demographics are shown in Tables 1 and 2. The overall intention-to-treat (ITT) SVR12 rate was 98.2% (165/168), with no virologic failures among non-cirrhotic patients treated for 8 weeks; mITT rate (excluding non-virologic failures) was 99.4% (167/168). Reasons for nonresponse were breakthrough (n = 1; patient with incomplete study drug adherence), premature study drug discontinuation (n = 1), and missing SVRL (n = 1). Safety analyses included 18 non-cirrhotic GT1b infected patients treated for 12 weeks (all achieved SVR12). AEs occurring in ≥5% of patients were fatigue, headache, nausea, and nasopharyngitis. Serious AEs and AEs leading to discontinuation were rare; none were related to study drug. Grade 3 or higher laboratory abnormalities were infrequent. All patients maintained HIV-1 suppression (<200 copies/ml) during treatment.

Conclusion. Ganclovir/pirenaltavir was highly efficacious and well tolerated in patients co-infected with HCV GT1-6/HIV-1 without or with cirrhosis following 8 or 12 weeks of treatment, respectively, and could be the first 8-week pan-genotypic treatment option for HCV/HIV-1 co-infected patients without cirrhosis.

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1966. Evaluating a Prototype Microbiome Health Index (MHI) as a Measure of Microbiome Restoration Using Data Derived From a Published Study of Fecal Microbiota Transplant (FMT) to Treat Recent Clostridium difficile Infections (rCDI)

Ken Blount, PhD1; Courtney Jones, BS2; Elena Deych, MS3 and Bill Shannon, PhD, MBA1; Rebiotix, Inc., Roseville, Minnesota, 2Research, Bardstown, Kentucky, 3Sanofi, Rebiotix, Inc.: Employee, Salary. 

Results. At baseline, 92% of patients in the FMT cohort were below the MHI = 8.2 cutpoint, consistent with a rCDI diagnosis. Among FMT responders 7 days after treatment, 91% of patients had shifted to MHI > 8.2 (P < 0.001 compared with baseline). Likewise, a significant shift was observed from baseline to 30 days (P < 0.0001), with 83% having MHI > 8.2. There were insufficient patients to support a statistical comparison of IBD vs. no IBD, but MHI trends lowered at all time points among patients with IBD.

Conclusion. MHI parameters derived from RBX2660 trials were predictive of pre- and post-treatment states for a published cohort of FMT-treated rCDI patients, suggesting that this totometric MHI represents a useful dysbiosis measure beyond RBX2660 trials. Lower MHI among patients co-diagnosed with IBD suggests the potential utility of MHI beyond rCDI. Collectively our results continue to support the utility of MHI and its prospective evaluation in ongoing Phase 3 clinical trials.

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1967. Study of the Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine (MenACYW-TT) When Co-administered with Other Vaccines in Healthy Adolescents

James Hedrick, MD1; Shane Christensen, MD2; Lee-Jah Chang, MD2; Judy Pan, PhD2; Emilia Jordano, MD2 and Manande Dhinghra, MD2; Kentucky Pediatric and Adult Research, Bardstown, Kentucky, 2J. Lewis Research, Salt Lake City, Utah, 3sanofi pasteur, Swiftwater, Pennsylvania

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Background. The MenACYW-TT conjugate vaccine is a quadrivalent meningo- coccal conjugate intended for global use in all age groups. This post hoc analysis of phase II study evaluated the safety and immunogenicity of the vaccine when compared with a licensed quadrivalent conjugated meningooccal vaccine (MCV4-CRM) when co-administered with tetanus, diphtheria, acellular pertussis (Tdap), and human papilloma virus (HPV4) vaccines in meningococcal vaccine naïve adolescents (10–17 years of age).

Methods. A randomized, open-label, multicenter study (NCT02196691) was conducted in 1,715 healthy subjects in the United States, who were randomly assigned to receive MenACYW-TT conjugate vaccine, MCV4-CRM, MenACYW-TT conjugate vaccine (co-administered with Tdap and HPV4), or Tdap and HPV4 vaccines. Serum bactericidal assay with human (hSBA) and baby rabbit (rSBA) complement was used to measure antibodies against serogroups A, C, W, and Y and test strains at baseline and 30 days after vaccination. Safety data were collected up to 6 months post-vaccination.

Results. Noninferiority of immune response was demonstrated between MenACYW-TT conjugate vaccine and MCV4-CRM, and MenACYW-TT conjugate vaccine when co-administered with Tdap and HPV4 vaccines vs. when administered alone, based on percentages of study participants achieving hSBA vaccine seroresponse at Day 30 from D0 baseline. The proportions of individuals with hSBA ≥1:8 after MenACYW-TT conjugate vaccine administration were higher than those after MCV4-CRM administration for all four serogroups (A: 93.5% vs. 82.8%; C: 98.5% vs. 76.0%; W: 99.1% vs. 90.7%; Y: 97.2% vs. 83.2%). Co-administration of MenACYW conjugate, Tdap and HPV4 vaccines did not generate any results suggestive of immune interfer- ence. Reactogenicity profiles were comparable across study groups. Most unsolicited adverse events were of Grade 1 or Grade 2 intensity. No vaccine related serious adverse events were reported.

Conclusion. MenACYW-TT conjugate vaccine was immunogenic and well tolerated when administered as a single dose to meningococcal vaccine naïve adolescents along with Tdap and HPV4 vaccines. Such a vaccine will offer an alternative for the prevention of invasive meningococcal disease in susceptible populations across the world.

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1968. Procalcitonin-Guided Antibiotic Therapy for Lower Respiratory Tract Infections in a US Academic Medical Center

Jennifer Townsend, MD1; Victoria Adams-Sommer, PharmD2; Panagis Galiatsatos, MD2; David Pearse, MD2; Flora Kisuule, MD2; Hardin Pantle, MD2; Mary Masterson, PA-C2; Catherine Kiruthi, PharmD2; Paul Ortiz, PharmD2; Elsen Jacob, PharmD2; Jacob Sama, MD2; Michael Meglat, MD2; Seema Nayak, MD2; Jillian Irwin, MD2; Cyrus Mazzuli, MD2; Sam Stern, MD2; Albert Aghaian, RN2; Robert Juran, RN2; Kevin Pioter, PhD, MPA2 and Robin McKenzie, MD2; Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland, 1Johns Hopkins Bayview Medical Center, Baltimore, Maryland, 2Pulmonary and Critical Care, Johns Hopkins Bayview Medical Center, Baltimore, Maryland, 3Hospital Medicine, Johns Hopkins Bayview Medical Center, Baltimore, Maryland, 4Emergency Medicine, Johns Hopkins Bayview Medical Center, Baltimore, Maryland, 5Pharmacy, Johns Hopkins Bayview Medical Center, Baltimore, Maryland, 6Medicine, Johns Hopkins Bayview Medical Center, Baltimore, Maryland

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Background. European trials using procalcitonin (PCT)-guided antibiotic therapy for patients with lower respiratory tract infections (LRTI) have resulted in significant reductions in antibiotic use without increasing adverse outcomes. Few prospective studies have examined PCT-guided antibiotic therapy for LRTI in the United States.