1947. Influenza Vaccination via Oral Tablet is Protective and Induces a Unique Mucosal Immune Response

Nikita Kolhatkar, PhD; Keith Gottlieb, PhD; Kassandra Kasparek, BS; Katie Hodgson, BS; Sean Tucker, PhD and David Liebowitz, MD, PhD; Vaxart, Inc., South San Francisco, California

Session: 227. Clinical Trials

Saturday, October 6, 2018: 12:30 PM

Background. Oral vaccines delivered as tablets offer several advantages over traditional injection-based vaccines including ease of distribution and administration as well as temperature-stable formulation options. Oral vaccination is also advantageous because it directly induces a strong mucosal response, which is thought to be critical for preventing future infections. Here we present results from a phase II clinical challenge study comparing efficacy of an oral recombinant adenovirus-based vaccine expressing hemagluttinin (HA) from A/California 04/09 to that of a commercial injectable quadrivalent (QIV) influenza vaccine.

Methods. In this 2016–2017 clinical trial (NCT02918006), subjects were immunized with either oral vaccine, QIV, or placebo and then challenged 90 days post-immunization with wildtype influenza A H1 virus to measure vaccine efficacy and durability. Protection was assessed by measuring changes in HAI titres, microneutralization, and IgA/IgG ASC assays. Additionally, exploratory flow cytometry evaluated quantitative and qualitative aspects of immunogenicity including markers of activation and mucosal homing on B cells. Analysis was performed on days 0 and 7 post-immunization and 0 and 6 days post-viral challenge. Plasmablasts sorted from PBMCs were then isolated for genomic DNA and sequenced for heavy chain receptor sequencing using NGS analysis.

Results. Of the subjects immunized with Vaxart's oral tablet vaccine, 48% were protected. QIV, by comparison, protected 38% of immunized individuals. Only 37% of Vaxart subjects developed influenza infection compared with 44% of QIV subjects and 71% of placebo subjects. While both vaccines induced a humoral immune response, FACS analysis and NGS revealed that Vaxart subjects had more activated plasmablasts expressing surface mucosal homing markers and a more diverse B cell population than QIV subjects.

Conclusion. Vaxart's oral influenza tablet vaccine protected against influenza infection as well or better than injectable QIV. However, the mechanism of protection appears to be unique to the route of immunization; oral immunization allows for specific homing of influenza specific B cells to sites of infection and produces a more diverse antibody repertoire.

Disclosures. **N. Kolhatkar**, Vaxart, Inc.: Employee, Salary. **K. Gottlieb**, Vaxart, Inc.: Employee, Salary. **K. Kasparek**, Vaxart, Inc.: Employee, Salary. **K. Hodgson**, Vaxart, Inc.: Employee, Salary. **S. Tucker**, Vaxart, Inc: Employee, Salary. **D. Liebowitz**, Vaxart, Inc.: Employee and Investigator, Salary.

1948. A Host-Response Assay Distinguishes Between Simple *Influenza* Patients and *Influenza* Patients With Bacterial Coinfection

Meital Paz, BSc[1]; Kfir Oved, PhD[1]; Tanya Gottlieb, PhD[1]; Asi Cohen, PhD[1]; Roy Navon, MSc[1]; Niv Mastboim, BSc[1]; Ellen Bamberger, MD[1,2,3]; Tom Friedman, MD[1,4]; Liat Etshtein, MD[1,4]; Olga Boico, PhD[1]; Isaac Srugo, MD[2,3]; Irina Chistyakov, MD[2,3]; Adi Klein, MD[3,5]; Israel Potasman, MD, FIDSA[3,6]; Eran Eden, PhD[1] and Liran Shani, MD[1]; [1]MeMed Diagnostics, Tirat Carmel, Israel, [2]Department of Pediatrics, Bnai-Zion Medical Center, Haifa, Israel, [3]Ruth and Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel, [4]Rambam Health Care Campus, Haifa, Israel, [5]Department of Pediatrics, Hillel Yaffe Medical Center, Hadera, Israel, [6]Infectious Diseases, Bnai Zion Medical Center, Haifa, Israel

Session: 227. Clinical Trials

Saturday, October 6, 2018: 12:30 PM

Background. Identifying bacterial coinfection in influenza patients can be difficult as the symptoms of simple influenza vs. mixed infections are often similar, leading to antibiotic overuse. A new host-response assay (ImmunoXpert™) that integrates the levels of three proteins (TRAIL, IP-10, and CRP) was shown to exhibit high performance in distinguishing between bacterial and viral disease in two double-blind validation studies. Here we sought to evaluate its ability to differentiate between simple influenza and influenza with bacterial coinfection.

Methods. The study population included 653 febrile pediatric and adult patients prospectively recruited in the "Curiosity" study. Patient etiology (simple viral vs. mixed infection) was determined by unanimous expert adjudication based on comprehensive clinical, laboratory and radiological assessment. Influenza strains (A or B) were detected using multiplex PCR applied to nasal swabs (Seeplex-RV15). We compared the expert panel diagnosis with the assay that gives three possible outcomes: viral, bacterial (including viral with bacterial coinfection) or equivocal. An equivocal outcome does not provide diagnostic information and is observed in ~10% of cases.

Results. Out of 653 patients, 51 had positive influenza detection and unanimous expert diagnosis: 44 simple viral infections and seven influenza with bacterial coinfections (Figure 1). Antibiotics were prescribed to all seven cases of influenza with bacterial coinfection and to 20/44 cases adjudicated as simple viral infections, indicating an overuse rate of 45%. The assay correctly classified 40 of the 44 simple viral cases (out of the remaining four, two were assigned viral with bacterial coinfection, and two received equivocal outcomes) as well as five of the seven viral with bacterial coinfection cases (the remaining two received equivocal outcomes) supporting the assay's potential to reduce antibiotic overuse 5-fold (from 45% to 4/44 = 9%, $P < 0.001$).

Conclusion. The host–response assay can differentiate between simple influenza and influenza patients with bacterial coinfection, with potential to reduce antibiotic overuse. Utility studies are warranted to demonstrate that the assay can safely assist physicians in correct management of influenza patients.

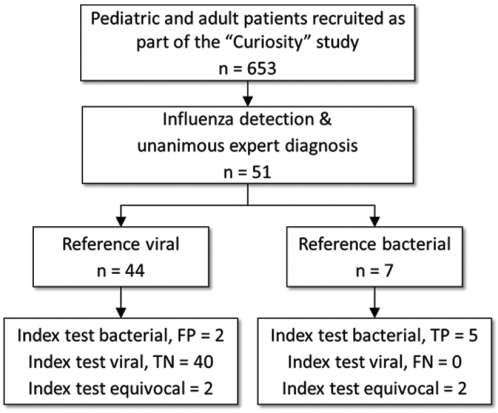

Figure 1. Flow through of febrile patients with positive influenza detection.
FP, false-positive; TN, true-negative; TP, true-positive; FN, false-negative.
The index test is available in Europe as ImmunoXpert™ (CE-IVD), not yet cleared by the FDA.

Disclosures. **M. Paz**, MeMed Diagnostics: Employee, Salary. **K. Oved**, MeMed Diagnostics: Board Member, Employee and Shareholder, Salary. **T. Gottlieb**, MeMed Diagnostics: Employee, Salary. **A. Cohen**, MeMed Diagnostics: Employee, Salary. **R. Navon**, MeMed Diagnostics: Employee, Salary. **N. Mastboim**, MeMed Diagnostics: Employee, Salary. **E. Bamberger**, MeMed Diagnostics: Employee, Salary. **T. Friedman**, MeMed Diagnostics: Employee, Salary. **L. Etshtein**, MeMed Diagnostics: Employee, Salary. **O. Boico**, MeMed Diagnostics: Employee, Salary. **I. Potasman**, MeMed Diagnostics: Holding stock options, Stock options. **E. Eden**, MeMed Diagnostics: Board Member, Employee and Shareholder, Salary. **L. Shani**, MeMed Diagnostics: Employee, Salary.

1949. Safety and Efficacy of Ambulatory Outpatient Treatment of Febrile Neutropenia in Children With Cancer in Mexico: A Multicenter Randomized Controlled Trial

Martha Avilés, MD, MSc[1]; Marta Zapata, MD, MSc[2]; Rómulo Rosales, MD[3]; Francisco Otero, MD[4]; Amilcar Valencia, MD[5]; Jose Peñaloza, MD[6] and Alfonso Reyes-Lopez, MsSc[7]; [1]Infectious Diseases, Hospital Infantil de Mexico Federico Gomez, Mexico City, Mexico, [2]Oncology, Instituto Nacional de Pediatria, Mexico city, Mexico, [3]Hospital Infantil de Mexico Federico Gomez, Mexico City, Mexico, [4]Infectious Diseases, Instituto Nacional de Pediatria, Mexico City, Mexico, [5]Infectious Diseases, Hospital Juárez de México, Mexico City, Mexico, [6]Oncology, Hospital Juárez de México, Mexico City, Mexico, [7]Hospital Infantil de Mexico, Federico Gomez, Mexico City, Mexico

Session: 227. Clinical Trials

Saturday, October 6, 2018: 12:30 PM

Background. Fever and neutropenia (FN) are frequent complications in children with cancer who receive chemotherapy. Although there is evidence of the efficacy of outpatient treatment, inpatient treatment is the standard of care in Mexico City. We aimed to determine whether sequential parenteral-oral outpatient treatment is non-inferior to intravenous inpatient treatment for children with FN in a middle-income setting.

Methods. Randomized controlled clinical trial in subjects 1 to 18 years old with low-risk FN in three hospitals in Mexico City. After 48 to 72 hours of cefepime inpatient treatment, subjects were eligible to participate if they were afebrile for at least 24 hours, had negative cultures and no source of infection. Subjects were randomly assigned to either continue receiving cefepime (inpatient arm) or start receiving cefixime (outpatient arm). Primary end point was treatment failure define as new onset fever, new source of infection or necessity of change antibiotic. Estimated sample size was 68 FN episodes per group. Parametric and nonparametric statistical analyses were performed for comparisons between groups.

Results. Between July 2015 and September 2017, a total of 1,237 episodes of FN were evaluated, of which 469 episodes were eligible. From these, 388 were excluded: 337 due to not meeting the inclusion criteria, eight parents refused to participate, four were evaluated after 72 hours of treatment and three were excluded for other reasons. Of the 117 randomized episodes, 59 were allocated into the outpatient arm and 58 into the inpatient arm. After randomization, demographic and clinical variables did not differ between groups. Treatment failure occurred in 6.9% (4) of patients in the inpatient arm vs. 0% in the outpatient arm ($P = 0.05$). Failures were associated to influenza B infection, catheter related blood stream infection and fever without a source. Mean duration of antibiotics was 4.6 days [SD (standard deviation) 4.5 days, C.I. 95% 3.5–5.8 days] in the outpatient arm and 4.4 days (SD 2.5 days, CI 95%, 3.7–5.0 days) in the inpatient arm ($P = 0.70$).

Conclusion. In our population, outpatient sequential, parenteral-oral treatment with cefixime seems to be as safe and efficacious as parenteral inpatient treatment of low-risk FN episodes.

Disclosures. **All authors:** No reported disclosures.

1950. Prevention of Recurrent *Clostridium difficile* at Six Months Following Treatment With Microbiota-Based Therapy RBX2660: Durability Results From a Phase 2 Open-Label Study

Sarah Mische, PhD[1]; Robert Orenstein, DO, FIDSA[2]; Erik R. Dubberke, MD, MSPH, FIDSA, FSHEA[3]; Sahil Khanna, MBBS, MS[4]; Gail Hecht, MD[5]; Herbert Dupont, MD, FIDSA[6]; Christine Lee, MD, FRCPC[7] and Ken Blount, PhD[1]; [1]Rebiotix, Inc., Roseville, Minnesota, [2]Infectious Diseases, Mayo Clinic Arizona, Phoenix, Arizona, [3]Washington University School of Medicine, St. Louis, Missouri, [4]Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, [5]Division of Gastroenterology and Nutrition, Loyola University Medical Center, Maywood, Illinois, [6]St. Luke's Hospital and Kelsey Research Foundation and Kelsey-Seybold Clinic, Houston, Texas, [7]McMaster University, Hamilton, ON, Canada

Session: 227. Clinical Trials

Saturday, October 6, 2018: 12:30 PM

Background. Numerous microbiota-based therapies are being evaluated for prevention of *C. difficile* infection (rCDI), a public health threat with high recurrence rates associated with the current standard of care. RBX2660, a standardized microbiota-based drug, was efficacious for preventing rCDI in a double-blinded Phase 2b clinical study (PUNCH CD 2). Herein we report the durability of RBX2660 beyond the initial primary clinical end-point of a subsequent Phase 2 open-label study, demonstrating rCDI prevention at 6 months post-treatment.

Methods. This prospective, multi-center, open-label Phase 2 study enrolled subjects who had experienced either ≥2 recurrences of CDI following standard-of-care antibiotic therapy or ≥2 episodes of severe CDI requiring hospitalization. Participants received up to two doses of RBX2660 delivered via enema with doses 7 days apart. The primary endpoint of the open-label clinical study defined efficacy as absence of CDI at 8 weeks from the last dose. Safety follow-ups and durability assessments occurred via telephone at 3, 6, 12, and 24 months. The study is ongoing, and not all subjects have completed their assessments.

Results. This study included 149 RBX2660-treated subjects and 110 historical control subjects from 31 and 4 centers, respectively, in the United States and Canada. At 8-weeks post-treatment, RBX2660's efficacy in preventing rCDI (79.9%; 119/149) was higher than CDI-free rates in the historical control group (51.8%, 57/110; $P < 0.001$). Of the 119 subjects who were determined to be treatment success at 8 weeks, 117 have data through 6 months, of which 8 were exited for non-CDI reasons. Of those 109 subjects through the 6-month follow-up, 3 (2.8%) had a new CDI beyond 8 weeks after enema. The 6-month long-term CDI-free rate was 97.2% (106/109) (median follow-up: 182 days; mean: 177 days).

Conclusion. RBX2660, a microbiota-based drug, was efficacious for the prevention of recurrent CDI with long-term durability at 6-months post-treatment; a result consistent with 6-month rCDI prevention reported for the Phase 2b PUNCH CD 2 trial. Long-term follow-up of RBX2660 safety and efficacy 24 months is ongoing.

This analysis was funded by Rebiotix Inc., Roseville, MN.

Disclosures. **S. Mische**, Rebiotix, Inc.: Employee, Salary. **R. Orenstein**, Rebiotix, Inc.: Scientific Advisor, Consulting fee. **E. R. Dubberke**, Rebiotix, Inc.: Scientific Advisor, Consulting fee. **S. Khanna**, Rebiotix, Inc.: Scientific Advisor, Consulting fee and Research support. **G. Hecht**, Rebiotix, Inc.: Scientific Advisor, Consulting fee. **H. Dupont**, Rebiotix, Inc.: Investigator, Research support. **C. Lee**, Rebiotix, Inc.: Scientific Advisor, Consulting fee. **K. Blount**, Rebiotix, Inc.: Employee, Salary.

1951. Nephrotoxicity Associated With Imipenem/Cilastatin/Relebactam (IMI/REL) vs. Imipenem/Cilastatin Plus Colistin (IMI+CST) in Patients With Imipenem-Nonsusceptible (NS) Bacterial Infections

Michelle Brown, RN[1]; Johann Motsch, MD[2]; Keith Kaye, MD, MPH[3]; Thomas File, MD[4]; Helen W. Boucher, MD, FIDSA[5]; Neika Vendetti, MPH[1]; Angela Aggrey, PhD[1]; Hee-Koung Joeng, PhD[1]; Robert Tipping, MS[1]; Jiejun Du, PhD[1]; Daryl D. Depestel, PharmD, BCPS-ID[1]; Joan Butterton, MD[1]; Nicholas A. Kartsonis, MD[1] and Amanda Paschke, MD, MSCE[1]; [1]Merck & Co., Inc., Kenilworth, New Jersey, [2]Universitätsklinikum Heidelberg, Heidelberg, Germany, [3]University of Michigan, Ann Arbor, Michigan, [4]Summa Health System, Akron, Ohio, [5]Infectious Diseases, Tufts Medical Center, Boston, Massachusetts

Session: 227. Clinical Trials

Saturday, October 6, 2018: 12:30 PM

Background. Nephrotoxicity is a common complication of CST-based therapy, limiting its use to treat carbapenem-resistant bacterial infections. REL is a novel β-lactamase inhibitor that restores imipenem activity against many imipenem-NS strains of Gram-negative pathogens. IMI/REL was shown to be as effective but better tolerated than IMI+CST in the phase 3 RESTORE-IMI 1 study (NCT02452047), including a lower incidence of treatment-emergent nephrotoxicity (prespecified secondary endpoint). Here we present additional renal safety data from that trial.

Methods. Randomized, active-controlled, double-blind, phase 3 trial in adults with infections caused by ≥1 imipenem-NS (but CST- and IMI/REL-susceptible) pathogen. Treatment (2:1) was IMI/REL or IMI+CST for 5–21 days in complicated intra-abdominal infection and complicated urinary tract infection and 7–21 days in hospital-acquired/ventilator-associated bacterial pneumonia. For baseline serum creatinine (Cr) <1.2 mg/dL, nephrotoxicity was defined as a doubling of serum Cr to >1.2 mg/dL OR decrease in Cr clearance [CrCl] ≥50%; for Cr ≥1.2 mg/dL, nephrotoxicity was defined as an increase in serum Cr ≥1 mg/dL OR decrease from baseline in CrCl ≥20% OR need for renal replacement therapy. KDIGO and RIFLE criteria of acute kidney injury (AKI) were applied to the data; renal-related adverse events (AEs) were analyzed.

Results. A total of 47 patients were randomized, treated (31 IMI/REL, 16 IMI+CST), and included in this analysis. A significantly smaller percentage of patients in the IMI/REL than the IMI+CST group experienced protocol-defined nephrotoxicity (% difference: −45.9 [95% CI: −69.1, −18.4]; $P = 0.002$) during study treatment and the 14-day follow-up period (table). These results were confirmed by applying KDIGO and RIFLE criteria, with no patients in the IMI/REL group in stage 3 AKI or failure compared with 31.3% and 25.0%, respectively, in the IMI+CST group. Fewer renal AEs, including discontinuations due to renal events, were observed in the IMI/REL group.

Conclusion. IMI/REL demonstrates a more favorable renal safety profile compared with CST-based therapy, as demonstrated by a lower incidence of treatment-emergent nephrotoxicity and AKI with IMI/REL across several different analyses.

Table. Protocol-specified nephrotoxicity and renal AEs

	IMI/REL N=31		IMI+CST[a] N=16	
	n/m	% (95% CI)	n/m	% (95% CI)
Protocol-specified nephrotoxicity	3/29	10.3 (2.8, 27.2)	9/16	56.3 (33.2, 76.9)
AKI (KDIGO)	**n/m**	**%**	**n/m**	**%**
Stage 1	5/29	17.2	6/16	37.5
Stage 2	1/29	3.4	2/16	12.5
Stage 3	0/29	0	5/16	31.3
AKI (RIFLE)	**n/m**	**%**	**n/m**	**%**
Risk	3/29	10.3	6/16	37.5
Injury	1/29	3.4	2/16	12.5
Failure	0/29	0	4/16	25.0
Renal AEs[b]	**n/m**	**%**	**n/m**	**%**
Blood Cr increased	0/31	0	4/16	25.0
Blood urea increased	0/31	0	1/16	6.3
CrCl decreased	2/31	6.5	2/16	12.5
GFR decreased	0/31	0	1/16	6.3
Acute kidney injury	1/31	3.2	0/16	0
Renal failure	1/31	3.2	0/16	0
Drug-related renal AEs leading to discontinuation of treatment	**n/m**	**%**	**n/m**	**%**
Blood Cr increased	0/31	0	1/16	6.3
CrCl decreased	0/31	0	1/16	6.3

[a]Provided as colistimethate sodium. [b]Based on investigator assessment.
GFR, glomerular filtration rate; n/m, number of patients with event of interest/number of patients evaluable (for nephrotoxicity and AKI, those with a baseline Cr measurement and ≥1 Cr measurement following ≥1 dose of study therapy).
Two IMI/REL patients with missing Cr values were excluded from nephrotoxicity/AKI analyses.
Protocol-specified nephrotoxicity: CrCl was estimated by Cockcroft Gault equation (Cockcroft DW, Gault MH. *Nephron.* 1976;16[1]:31-41).
KDIGO (Kidney Disease: Improving Global Outcomes) Criteria: KDIGO Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int Suppl.* 2012 Mar;2(1):1-138.
RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) Criteria: GFR was estimated based on the Chronic Kidney Disease Epidemiology Collaboration equation (Levey AS, et al. *Ann Intern Med*. 2009;150[9]:604-612).

Disclosures. **M. Brown**, Merck & Co., Inc.: Employee, Salary. **J. Motsch**, Heidelberg University: Research Contractor, Research grant. **K. Kaye**, Merck & Co., Inc.: Consultant and Research Contractor, Research grant. Melinta, Achaogen, Allergan: Consultant, Consulting fee. **T. File**, Bio Merieux, Curetis, Melinta, Merck, MotifBio, Nabriva, Paratek, Pfizer: Consultant, Consulting fee. **H. W. Boucher**, Merck & Co., Inc.: Scientific Advisor, Consulting fee. **N. Vendetti**, Merck & Co., Inc.: Employee, Salary. **A. Aggrey**, Merck & Co., Inc.: Employee, Salary. **H. K. Joeng**, Merck & Co., Inc.: Employee, Salary. **R. Tipping**, Merck & Co., Inc.: Employee, Salary. **J. Du**, Merck & Co., Inc.: Employee, Salary. **D. D. Depestel**, Merck & Co., Inc.: Employee, Salary. **J. Butterton**, Merck & Co., Inc.: Employee, Salary and Stock. **N. A. Kartsonis**, Merck & Co., Inc.: Employee, Salary and Stocks. **A. Paschke**, Merck & Co., Inc.: Employee and Shareholder, Salary.

1952. Evaluation of Relapse and Reinfection Using Whole-Genome Sequencing of *Clostridium difficile* Isolates From Elderly Patients With *C. difficile* Infection (CDI) in the EXTEND Randomized, Controlled, Comparative Study of Extended-Pulsed Fidaxomicin and Vancomycin for the Treatment of CDI

Mark Wilcox, MD[1,2]; Oliver A. Cornely, MD[3]; Benoit Guery, MD[4]; Chris Longshaw, PhD[5]; Areti Georgopali, MD[5]; Andreas Karas, MD[6]; Gbenga Kazeem, PhD[7]; Jose Alejandro Palacios-Fabrega, PhD[7] and Maria J.G.T. Vehreschild, MD[8]; [1]Leeds Teaching Hospitals and University of Leeds, Leeds, UK, [2]Leeds Institute of Biomedical and Clinical Sciences, University of Leeds, Leeds, UK, [3]Clinical Trials Centre Cologne (ZKS Köln), Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases, University of Cologne, Cologne, Germany, [4]University Hospital and University of Lausanne, Lausanne, Switzerland, [5]Astellas Pharma, Inc., Chertsey, UK, [6]Astellas Pharma Ltd., Chertsey, UK, [7]Astellas Pharma Europe Ltd., Chertsey, UK, [8]University Hospital of Cologne and German Centre for Infection Research, Partner Site Bonn-Cologne, Cologne, Germany

Session: 227. Clinical Trials

Saturday, October 6, 2018: 12:30 PM

Background. The EXTEND study demonstrated reduced 90-day recurrence rates for an extended-pulsed regimen of fidaxomicin (EPFX) vs. standard vancomycin (SV) in the treatment of *Clostridium difficile* infection (CDI): treatment difference −13%, $P = 0.00073$.[1] Whole-genome sequencing (WGS) is used to differentiate between