Lucy Ward, DMV, Ph.D.[12]; Rachel Overman, MD[12]; Janice M. Rusnak, M.D.[13]; Callie Bounds, Ph.D.[14]; Christopher Badorrek, Ph.D.[15]; Christina Polyak, MD MPH[16]; Allahna L. Esber, PhD[16]; Amber D. Moodley, MPH[17]; Chi Tran, BSN[18]; Auguste Gaddah, PhD[19]; Kerstin Luhn, PhD[20]; Macaya Douoguih, MD, MPH[10]; Cynthia Robinson, MD[20]; Julie A. Ake, MD[21]; [1]Walter Reed National Military Medical Center, Rockville, Maryland; [2]Makerere university Walter Reed Project, Kampala, Kampala, Uganda; [3]Henry M. Jackson Foundation Medical Research International, Kenya; U.S. Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, Maryland, USA, Kericho, Rift Valley, Kenya; [4]Henry M. Jackson Foundation Medical Research International, Kenya; Kenya Medical Research Institute/U.S. Army Medical Research Directorate-Africa/Kenya, Kisumu, Nyanza, Kenya; [5]National Institute for Medical Research-Mbeya Medical Research Center, Mbeya, Tanzania, Mbeya, Mbeya, Tanzania; [6]Instituto Nacional de Saúde, Maputo, Maputo, Mozambique; [7]U.S. Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD, USA, Silver Spring, Maryland; [8]Clinical Trials Center, Walter Reed Army Institute of Research, Silver Spring, Maryland, USA, Silver Spring, Maryland; [9]Walter Reed Army Institute of Research, Silver Spring, Maryland; [10]Janssen Vaccines and Prevention, Leiden, Netherlands, Leiden, Zuid-Holland, Netherlands; [11]US Military HIV Research Program/HJF, Bethesda, Maryland; [12]U.S. Department of Defense (DOD) Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense (JPEO-CBRND), Joint Project Manager for Chemical, Biological, Radiological, and Nuclear Medical (JPM CBRN Medical), Fort Detrick, Maryland, USA, Fort Detrick, Maryland; [13]Contract Support for U.S. Department of Defense (DOD) Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense (JPEO-CBRND), Joint Project Manager for Chemical, Biological, Radiological, and Nuclear Medical (JPM CBRN Medical),, Fort Detrick, Maryland; [14]Joint Project Manager for Chemical, Biological, Radiological, and Nuclear Medical, Fort Detrick, Maryland; [15]Contract Support for U.S. Department of Defense (DOD) Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense (JPEO-CBRND), Joint Project Manager for Chemical, Biological, Radiological, and Nuclear Medical (JPM CBRN Medical), Fort Detrick, Maryland, USA, Fort Detrick, Maryland; [16]The Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda, MD and Walter Reed Army Institute of Research, Silver Spring, MD, Bethesda, Maryland; [17]U.S. Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, Maryland; Henry M. Jackson Foundation for the Advancement of Military Medicine. Bethesda, Maryland, USA, Rockville, Maryland; [18]HJF/MHRP, Silver Spring, Maryland; [19]Janssen Research and Development, Beerse, Antwerpen, Belgium; [20]Janssen Vaccines and Prevention, Leiden, Zuid-Holland, Netherlands; [21]Walter Reed Army Institute of Research, Silver Spring, MD, Silver Spring, Maryland

Session: P-60. New Vaccines

Background. Ebola Virus Disease (EVD) outbreaks primarily occur in the HIV endemic setting of Sub-Saharan Africa. Transient increases in HIV viral load (VL), or blips, have been described following routine vaccinations. We characterized VL blips among PLWH enrolled in a phase 2 trial of a heterologous two-dose EVD vaccine.

Methods. In EBL2003, adult participants with and without HIV were randomized 1:4 to receive placebo or vaccine. Part A in the US studied MVA-BN-Filo followed by Ad26.ZEBOV 14 days later. Part B in Africa evaluated this MVA/Ad26 regimen and also a schedule of Ad26.ZEBOV followed by MVA-BN-Filo 29 days later. VL was assessed at screening, pre-vaccination, and 21, 42, 180, and 365 days post dose 2. Participants with VL < 20 copies/mL at the first 2 visits who received both doses and had complete VL data through 42 days post dose 2 were evaluated. Blips were defined as a post-injection VL ≥ 20 copies/mL no later than 42 days post dose 2, with subsequent return to VL < 20 copies/mL.

Results. A total of 277 PLWH on antiretroviral therapy (ART) were assessed; 73.3% (203) had baseline virologic suppression, and 89.2% (181) of those received both doses with complete VL data for inclusion in the analysis. Overall, 19.9% (36) experienced blips: 20.0% (29) of vaccinees vs 19.4% (7) of placebo recipients (p=1.0). All baseline suppressed participants with post-injection viremia subsequently regained suppression. Among vaccinees, the mean blip VL was 192 copies/mL, and the mean blip duration was 56 days, which was not significantly different from placebo. Of all blips, only 2 were > 1,000 copies/mL. Blips occurred in 24.0% (25) of Ad26/MVA recipients, and 9.7% (4) of MVA/Ad26 recipients (p=0.07). A dose of Ad26 was associated with a blip in 6.9% (10) of recipients vs 13.1% (19) for MVA recipients (p=0.12). Regardless of regimen, dose 1 was associated with a blip in 8.3% (12) of vaccinees, compared to 11.7% (17) of vaccinees for dose 2 (p=0.43).

Conclusion. Among successfully treated PLWH, we observed low magnitude post-dose HIV blips that were not more common in vaccine vs. placebo recipients and did not result in loss of virologic suppression. This data is favorable for the deployment of the EVD vaccines in this trial in areas of high HIV endemicity.

Disclosures. **Benjamin L. Custer, M.D.**, **Alexion Pharmaceuticals** (Shareholder)**Armata Pharmaceuticals** (Shareholder)**Biomarin Pharmaceutical** (Shareholder)**Crispr Therapeutics** (Shareholder)**CVS Health Corp** (Shareholder)**Editas Medicine** (Shareholder)**Gilead** (Shareholder)**Glaxo Smith Kline** (Shareholder)**Hologic Inc** (Shareholder)**Merck** (Shareholder)**Mesoblast LTD** (Shareholder)**Pfizer** (Shareholder)**Sanofi** (Shareholder)**Unitedhealth Group** (Shareholder)**Vertex Pharmaceuticals** (Shareholder) **Georgi Shukarev, MD**, **Janssen** (Employee) **Auguste Gaddah, PhD**, **Janssen Pharmaceutica N.V** (Employee) **Kerstin Luhn, PhD**, **Janssen Vaccines and Prevention** (Employee, Shareholder) **Macaya Douoguih, MD, MPH**, **Janssen** (Employee) **Cynthia Robinson, MD**, **Janssen Vaccines** (Employee)

1050. Phase 3 Trial to Evaluate the Safety, Tolerability, and Immunogenicity of V114 Followed by 23valent Pneumococcal Polysaccharide Vaccine 6 Months Later in At-risk Adults Aged 18–49 Years (PNEU-DAY): A Subgroup Analysis by Baseline Risk Factors

Laura Hammitt, MD[1]; Dean Quinn, BSc(Hons), MBChB[2]; Ewa Janczewska, MD, PhD, DSc[3]; Francisco J. Pasquel, MD, MPH[4]; Richard Tytus, BSc Phm, MD[5]; K. Rajender Reddy, MD[6]; Katia Abarca, MD[7]; Ilsiyar M. Khaertynova, MD[8]; Ron Dagan, MD[9]; Rachel Dawson, D.O. MPH[10]; Jennifer McCauley, BSc[10]; Kyeongmi Cheon, Ph.D.[10]; Alison Pedley, PhD[10]; Tina Sterling, BS[10]; Gretchen Tamms, B.S.[10]; Luwy Musey, MD[10]; Ulrike K. Buchwald, MD, MS[10]; [1]Johns Hopkins, Baltimore, MD; [2]P3 Research, Wellington Clinical Trial Research Unit, Wellington, Wellington, New Zealand; [3]The School of Health Sciences in Bytom, Medical University of Silesia, Bytom, Slaskie, Poland; [4]Emory, University School of Medicine, Atlanta, Georgia; [5]McMaster University, Hamilton, Ontario, Canada; [6]Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; [7]Escuela de Medicina, Pontificia Universidad Catolica de Chile, Santiago, Region Metropolitana, Chile; [8]Department of Infectious Diseases, Kazan State Medical Academy, Kazan, Tatarstan, Russia; [9]Ben-Gurion University of the Negev, Beer Sheva, HaDarom, Israel; [10]Merck & Co., Inc., Kenilworth, New Jersey

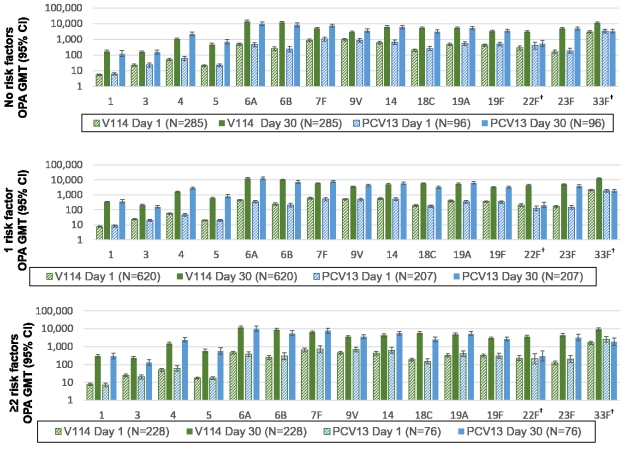
Session: P-60. New Vaccines

Background. Risk factors (RFs) for pneumococcal disease (PD) in immunocompetent individuals include comorbidities, behavioral habits, or living in a community with increased risk of PD transmission. RF stacking of comorbidities is associated with a higher incidence of PD, approaching that of immunocompromised individuals. Pneumococcal vaccination of certain adults is recommended with the 23-valent pneumococcal polysaccharide vaccine (PPSV23) alone/sequentially with pneumococcal conjugate vaccine (PCV). V114, an investigational 15-valent PCV, contains 2 epidemiologically important serotypes (STs), 22F and 33F, in addition to the 13 STs in 13-valent PCV (PCV13).

Methods. PNEU-DAY was a Phase 3 study evaluating V114 or PCV13 administered on Day 1, and PPSV23 given 6 months later, in adults aged 18–49 years with or without RFs. This subgroup analysis assessed safety, tolerability, and immunogenicity of V114 and PCV13 based on the number of baseline PD RFs, which included chronic liver, lung, and heart disease, diabetes mellitus, tobacco use, and alcohol consumption. Adverse events (AEs; overall and solicited) were collected after each vaccination. Immunogenicity assessment was based on ST-specific opsonophagocytic activity (OPA) at 30 days after each vaccination. Subgroup analyses were conducted by RF group (0, 1, or ≥2 RFs for PD).

Results. Among the 1515 participants randomized to V114 (n=1135) or PCV13 (n=380), 25.2% had no RFs, 54.7% had 1 RF and 20.1% had ≥2 RFs for PD at baseline. The proportions of participants with solicited AEs following V114/PCV13 and PPSV23 were comparable across the 3 subgroups, with injection-site pain, myalgia, and fatigue being the most common. V114 and PCV13 were immunogenic in all subgroups based on OPA geometric mean titers (GMTs) at 30 days post-vaccination for the 13 shared STs (**Figure**); in addition, V114 induced a robust immune response to the 2 unique STs (22F, 33F) in all subgroups. PPSV23 following PCV was immunogenic for all 15 STs contained in V114 across all subgroups.

Figure. Serotype-specific OPA GMTs at baseline and 30 days post-vaccination with V114 and PCV13 by number of baseline risk factors (per-protocol population)



†Serotypes not included in PCV13.

The within-group 95% CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution. Per protocol, Day 1 is pre-vaccination with PCV, Day 30 is 30 days following vaccination with PCV. Risk factors include chronic lung disease, tobacco use, diabetes mellitus, chronic liver disease, chronic heart disease, or alcohol consumption. N is the number of participants randomized and vaccinated with PCV.

CI, confidence interval; GMT, geometric mean titer (1/dilution); OPA, opsonophagocytic activity; PCV, pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; V114, 15-valent pneumococcal conjugate vaccine.

Conclusion. V114 administered alone/sequentially with PPSV23 is well tolerated and immunogenic for all 15 vaccine STs, including those not contained in PCV13, in immunocompetent adults aged 18–49 years, regardless of the number of baseline RFs.

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1051. Characterization of Immune Responses to a Live-Attenuated Tetravalent Dengue Vaccine

Ralph Braun, PhD[1]; Mayuri Sharma, PhD[1]; Christina DeMaso, n/a[1]; Allan Parker, n/a[1]; David Dominguez, n/a[1]; Heather Watkins, n/a[1]; Hansi Dean, PhD[1]; Lovkesh Karwal, n/a[1]; Eduardo Nascimento, n/a[1]; Nicole Messere, n/a[1]; Isamu Tsuji, n/a[1]; Melissa Zahralban-Steele, n/a[1]; Jeffrey R. Currier, PhD[2]; Heather Friberg-Robertson, PhD[2]; [1]Takeda Pharmaceuticals, Stow, Massachusetts; [2]Walter Reed Army Institute of Research, Silver Spring, Maryland

DEN-203, 204 and 205 study groups

Session: P-60. New Vaccines

Background. A safe and effective vaccine against dengue is needed to address an unmet medical need that affects a large portion of the world's population. Takeda's live attenuated tetravalent dengue vaccine candidate (TAK-003) has shown protection in an ongoing Phase 3 efficacy trial. TAK-003 contains an attenuated dengue type 2 virus (DENV-2), and 3 genetically modified viruses in which the structural proteins from each of the serotypes 1, 3 and 4 have been placed into the DENV-2 backbone. Exploratory immunological assessments have been a part of the TAK-003 clinical development plan to better understand the mechanisms of action of TAK-003, and to identify immune response signatures that may correlate with protection.

Methods. Cellular and humoral immune responses elicited by vaccination in dengue-naïve and dengue-exposed individuals were measured across several clinical trials. For the humoral response, several methods were used to measure the magnitude and characteristics of the antibodies following vaccination with TAK-003 including studies of neutralizing antibodies, antibodies that bind to the viral components of the vaccine, the affinity and complement fixing capabilities of antibodies specific to structural proteins, and additionally the level of antibodies specific to nonstructural protein 1 (NS1).

Results. A multifunctional cellular immune response was found following vaccination that primarily targeted nonstructural proteins in the DENV-2 backbone and was cross reactive to epitopes found in the other serotypes. The vaccine elicited neutralizing antibodies with high tetravalent seropositivity rates among participants. Further assessment of this response revealed that it consists of serotype-specific and cross-reactive neutralizing antibodies against all four serotypes. In addition, sera from vaccinated individuals neutralized genotypically diverse dengue strains. In addition to antibodies specific to structural components, antibodies to DENV-2 NS1 that were cross reactive to the NS1 proteins of the other serotypes were found.

Conclusion. The breadth of the cellular and humoral immune responses elicited by TAK-003 in vaccine recipients across a wide age range living in different endemicities aligns with the response profile expected of a multivalent live vaccine.

Disclosures. **Ralph Braun, PhD**, **Takeda Pharmaceuticals** (Employee) **Mayuri Sharma, PhD**, **Takeda Pharmaceuticals** (Employee) **Christina DeMaso, n/a**, **Takeda Pharmaceuticals** (Employee) **Allan Parker, n/a**, **Takeda Pharmaceuticals** (Employee) **David Dominguez, n/a**, **Takeda Pharmaceuticals** (Employee) **Heather Watkins, n/a**, **Takeda Pharmaceuticals** (Employee) **Hansi Dean, PhD**, **Takeda Pharmaceuticals** (Consultant) **Lovkesh Karwal, n/a**, **Takeda Pharmaceuticals** (Employee) **Eduardo Nascimento, n/a**, **Takeda Pharmaceuticals** (Employee) **Nicole Messere, n/a**, **Takeda Pharmaceuticals** (Employee) **Isamu Tsuji, n/a**, **Takeda Pharmaceuticals** (Employee) **Melissa Zahralban-Steele, n/a**, **Takeda Pharmaceuticals** (Employee) **Jeffrey R. Currier, PhD**, **Takeda Pharmaceuticals** (Scientific Research Study Investigator) **Heather Friberg-Robertson, PhD**, **Takeda Pharmaceuticals** (Scientific Research Study Investigator)

1052. Characterisation of the DNA binding properties of ridinilazole, a selective antibiotic currently in phase III trials for the treatment of *Clostridioides difficile*

Clive Mason, PhD[1]; Tim Avis, n/a[1]; Chris Coward, PhD[1]; David Powell, PhD[1]; Esther Duperchy, PhD[1]; Chenlin Hu, PhD[2]; M. Jahangir Alam, PhD[3]; Khurshida Begum, PhD[3]; Kevin W. Garey, Pharm.D., M.S., FASHP[3]; Stefanie Reich, PhD[4]; Stephen Moss, n/a[4]; [1]Summit Therapeutics, Cambridge, England, United Kingdom; [2]University of Houston, Houston, Texas; [3]University of Houston College of Pharmacy, Houston, Texas; [4]Domainex, Cambridge, England, United Kingdom

Session: P-61. Novel Agents

Background. *Clostridioides difficile* infection (CDI) is recognised by the CDC as an "urgent threat" in the USA, responsible for nearly 13,000 deaths, and carries an economic burden ranging from $5.4 to $6.3 billion per year. In a phase II study, ridinilazole was shown to be effective at treating CDI and decreasing subsequent recurrence compared to vancomycin. However, the precise mechanism of action of ridinilazole has yet to be fully elucidated. We now present data that reveals ridinilazole clearly co-localises with DNA in *C. difficile* and binds with high affinity to the minor groove of DNA. These interactions are predicted to have consequences on cellular functions within *C. difficile*.

Methods. High resolution confocal microscopy was used to track the intracellular localisation of ridinilazole in *C. difficile.* Fluorescence intensity was used to characterise the DNA binding properties of ridinilazole; sequence specificity was demonstrated with AT- or GC-rich DNA polymers, and tight binding was shown using short double-stranded oligonucleotides. Hanging drop vapour diffusion enabled co-crystallisation and subsequent structural determination of DNA-bound ridinilazole.

Results. Confocal microscopy revealed clear co-localisation of ridinilazole to the DNA within *C. difficile.* Ridinilazole demonstrated a dose-dependent increase in fluorescence in response to increasing concentration of target DNA. Fluorescence binding studies revealed that ridinilazole shows a preference towards AT-rich DNA sequences. Tight binding characteristics were demonstrated by ridinilazole in complex with short double-stranded oligonucleotides, returning dissociation constants (K_d) of 20 – 50 nM. Crystallisation enabled co-structures of ridinilazole bound to the minor groove of double-stranded DNA oligonucleotides to be solved.

Conclusion. Ridinilazole demonstrates tight binding with sequence specificity within the minor groove of DNA and co-localises with DNA in *C. difficile*. Further analysis is ongoing to fully understand this novel mechanism of action, the downstream consequences of these interactions and how they contribute to the bactericidal activity of ridinilazole.

Disclosures. **Clive Mason, PhD**, **Summit Therapeutics** (Employee, Shareholder) **Tim Avis, n/a**, **Summit therapeutics** (Shareholder) **Chris Coward, PhD**, **Summit Therapeutics** (Employee, Scientific Research Study Investigator, Shareholder) **David Powell, PhD**, **Summit Therapeutics** (Employee) **Kevin W. Garey, Pharm.D., M.S., FASHP**, **Summit Therapeutics** (Research Grant or Support)

1053. The β-Lactamase Inhibitor QPX7728 Restores the Activity of β-Lactam Agents against Contemporary Extended-Spectrum β-lactamase (ESBL)-Producing and Carbapenem-Resistant *Enterobacterales* (CRE) Isolates, Including Isolates Producing Metallo-β-lactamases

Jill Lindley[1]; Yahse Edah, AS[1]; Olga Lomovskaya, PhD[2]; Mariana Castanheira, PhD[1]; Mariana Castanheira, PhD[1]; [1]JMI Laboratories, North Liberty, Iowa; [2]Qpex Biopharma, San Diego, California

Session: P-61. Novel Agents

Background. The β-lactam (BL)/ β-lactamase inhibitor (BLI) combinations approved in the last 10 years are active against most ESBL-producing *Enterobacterales* (ENT) and CRE isolates, but have limited activity against metallo-β-lactamase (MBL)-producing ENT. We evaluated the activity of QPX7728 (QPX), a novel BLI with intravenous (IV) and oral availability, in combination with BL agents. We tested ENT isolates carrying the most common BL genes such as bla_{CTX-M}, transferable AmpCs, oxacillinases, MBLs, and serine carbapenemases.

Methods. A total of 1,027 ENT isolates were susceptibility (S) tested by reference broth microdilution against aztreonam (ATM), cefepime (FEP), cefdinir (CDR), ceftibuten (CTB), ceftolozane (CT) and piperacillin (PT) with fixed 4 mg/L of tazobactam, biapenem (BPM), meropenem (MER), and tebipenem (TEB) combined with QPX at fixed 4 and 8 mg/L. All isolates were genetically characterized using whole genome sequencing and included 520 ESBL-producers and 507 CRE with 168 producing MBLs.

Results. BL agents tested alone had limited activity against this challenge set of isolates (MIC_{90}, ≥32 mg/L); however, MIC_{90} values decreased ≥32-fold with the addition of QPX at the highest concentration tested (Table). Oral agents, CTB,CDR and TEB were tested with QPX at a fixed 4 mg/L and showed a 32- to 128-fold increase in potency (MIC_{90}, 0.5-4 mg/L). ATM and FEP were tested with QPX at a fixed 4 and 8 mg/L and displayed MIC_{90} values ranging from 0.12-0.5 mg/L. ATM and FEP, tested with 8 mg/L of QPX, inhibited 99.8% of isolates at the breakpoint for the BL agent alone. BLI inhibitor combinations PT and CT displayed MIC_{90} values of 2 and 4 mg/L with the addition of 8 mg/L QPX. MER with QPX at a fixed 4 mg/L and 8 mg/L inhibited 99.8% and 100% of isolates, respectively.

Conclusion. The activity of all BLs evaluated was restored when combined with QPX tested against this challenging collection of 1,027 ENT isolates displaying various