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.

Disclosures. **Laura Hammitt, MD**, **MedImmune** (Grant/Research Support, Scientific Research Study Investigator, Research Grant or Support)**Merck & Co., Inc.** (Grant/Research Support, Scientific Research Study Investigator, Research Grant or Support)**Novavax** (Grant/Research Support, Scientific Research Study Investigator, Research Grant or Support)**Pfizer** (Grant/Research Support, Scientific Research Study Investigator, Research Grant or Support) **Francisco J. Pasquel, MD, MPH**, **Boehringer Ingelheim** (Consultant)**Dexcom** (Grant/Research Support)**Eli Lilly & Company** (Consultant)**Insulet** (Grant/Research Support)**Merck & Co., Inc.** (Consultant, Grant/Research Support) **K. Rajender Reddy, MD**, **BMS** (Grant/Research Support)**Deciphera** (Advisor or Review Panel member)**Gilead** (Grant/Research Support)**Grifols** (Grant/Research Support)**HCC-TARGET** (Grant/Research Support)**Intercept** (Grant/Research Support)**Mallinckrodt** (Grant/Research Support, Advisor or Review Panel member)**NASH-TARGET** (Grant/Research Support)**Pfizer** (Advisor or Review Panel member)**Sequana** (Grant/Research Support) **Ron Dagan, MD**, **Medimmune/AstraZeneca** (Grant/Research Support, Scientific Research Study Investigator, Research Grant or Support)**MSD** (Consultant, Grant/Research Support, Scientific Research Study Investigator, Advisor or Review Panel member, Research Grant or Support, Speaker's Bureau)**Pfizer** (Consultant, Grant/Research Support, Scientific Research Study Investigator, Advisor or Review Panel member, Research Grant or Support, Speaker's Bureau) **Rachel Dawson, D.O. MPH**, **Merck & Co., Inc.** (Employee, Shareholder) **Jennifer McCauley, BSc**, **Merck & Co., Inc.** (Employee) **Kyeongmi Cheon, Ph.D.**, **Merck & Co., Inc.** (Employee, Shareholder) **Alison Pedley, PhD**, **Merck & Co., Inc.** (Employee) **Tina Sterling, BS**, **Merck & Co., Inc.** (Employee, Shareholder) **Gretchen Tamms, B.S.**, **Merck Sharp and Dohme** (Employee, Shareholder) **Luwy Musey, MD**, **Merck & Co., Inc.** (Employee) **Ulrike K. Buchwald, MD, MS**, **Merck & Co., Inc.** (Employee)**TB Alliance** (Employee)

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