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Session: 83. Late Breaker Oral Abstract Session 1
Thursday, October 3, 2019: 2:45 PM

Background. ACX-362E, a novel DNA polIIIC inhibitor, is a narrow-spectrum antibacterial selectively active against certain Gram-positive bacteria, including *Clostridioides difficile* (MIC_{90} = 4 µg/mL). The objectives of this phase I study was to assess the safety, pharmacokinetics, and fecal microbiome effects of ACX-362E

Methods. This three-part FIH phase 1, double-blind, randomized healthy volunteer trial determined the safety profile, food effect, and systemic/stool pharmacokinetics of escalating single (150, 300, 600, and 900 mg) and multiple (300 and 450 mg) doses of oral ACX-362E vs. placebo (PBO). Fecal microbiome effects (metagenomic sequencing and qPCR) of multiple-dose ACX-362E were compared with 6 subjects receiving concomitant open-label vancomycin 125 mg four times daily. Dose escalation to each new cohort occurred following review of safety and PK data by a safety oversight committee.

Results. Forty-four subjects received ACX-362E (single dose = 24, multiple doses = 12, food effect = 8) and 12 PBO. Overall, ACX-362E was well tolerated at all dose levels. Adverse events were generally mild and transitory, and no moderate, severe, cumulative, or dose-limiting drug-related adverse events leading to discontinuation were observed. Mean plasma half-life was approximately 2 hours and no accumulation occurred with repeated dosing (Figure 1). Systemic exposure was less than 1 µg/mL and decreased with food. Fecal concentrations during multiple dosing exceeded the *C. difficile* MIC by multiples of up to ~2,500. ACX-362E had minimal effect on Bacteroidetes phylum and caused significantly less dysbiosis than vancomycin (Figure 2).

Conclusion. This FIH clinical trial with ACX-362E demonstrated a favorable safety profile, low systemic and high fecal concentrations, and favorable gut microbiome changes compared with vancomycin. These results shows promise for further clinical development to treat *C. difficile* infections.

Figure 1: **Mean concentration-time profiles - Day 10, linear scale**

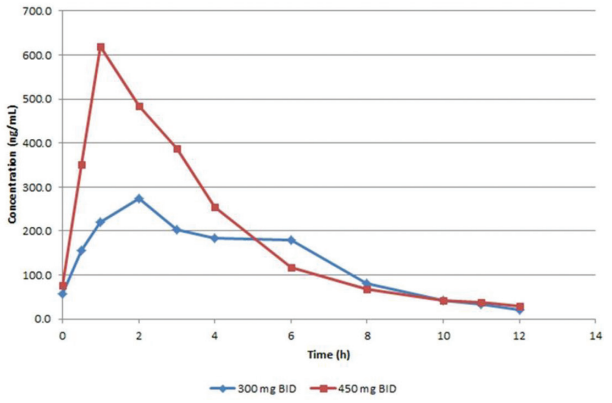
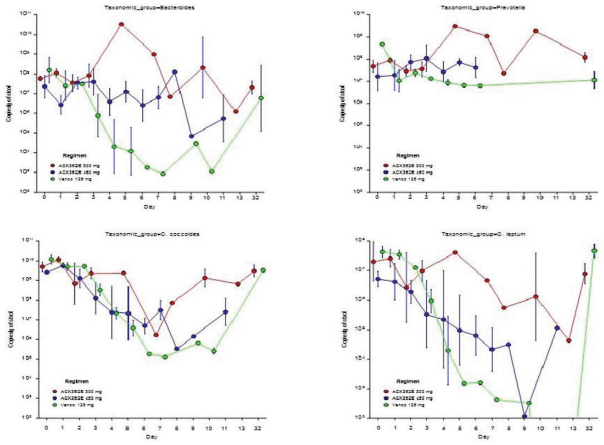


Figure 2. Microbiota levels belonging to different taxonomic groups measured by qPCR in samples



Disclosures. Kevin W. Garey, MS, PharmD, Acurx (Grant/Research Support), Martin Kankam, MD, PhD, MPH, Acurx Pharmaceuticals, LLC (Research Grant or Support), Julie Mercier, BS, Acurx Pharmaceuticals, LLC (Research Grant or Support), Corinne Seng Yue, BPharm, MSc, PhD, Acurx Pharmaceuticals, LLC (Grant/Research Support), Murray Ducharme, PharmD, Acurx Pharmaceuticals, LLC (Grant/Research Support), Anne J. Gonzales-Luna, PharmD, no financial relationships or conflicts of interest, M Jahangir Alam, PhD, No financial relationships or conflicts of interest, Khurshida Begum, PhD, No financial relationships or conflicts of interest, Michael Silverman, MD, Acurx Pharmaceuticals, LLC (Consultant, Employee, Shareholder).

LB8. Microarray Patch Delivery of Long-Acting HIV PrEP and Contraception

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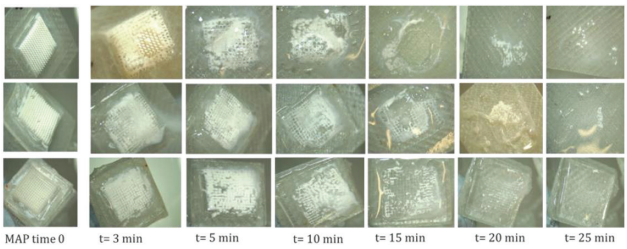
Session: 184. Late Breaker Oral Abstract Session 2
Friday, October 4, 2019: 1:45 PM

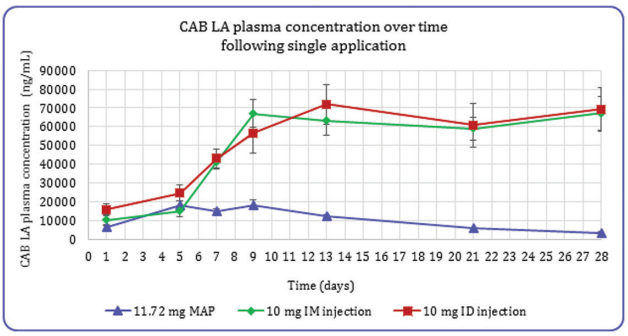
Background. The purpose of this research was to develop a microarray patch (MAP; also known as a microneedle patch) for delivery of long-acting cabotegravir (CAB LA) for HIV pre-exposure prophylaxis (PrEP) and co-delivery of long-acting CAB LA and a hormonal contraceptive to enable a future multi-purpose prevention technology. This abstract presents preclinical pharmacokinetic results of MAP delivery of CAB LA.

Methods. MAPs are an alternative delivery technology in clinical development for intradermal delivery of vaccines and pharmaceuticals. A MAP consists of an array of micron-scale projections (<1 mm in height) amassed on a baseplate and applied to the skin like a bandage. MAPs could provide a discreet delivery system that enables self-administration, which could be particularly important for HIV prevention and contraception for young women and girls in low-resource settings. The purpose of this 3-year, USAID-funded project is to develop a MAP for delivery of long-acting HIV PrEP through to the point of Phase I clinical readiness. Key attributes of the MAP for long-acting HIV PrEP, as defined by our target product profile, include patch size similar to commercially available transdermal patches (20 to 140 cm^2), wear-time of less than 24 hours (ideally 20 minutes), weekly or monthly administration to achieve therapeutic efficacy, and ideally successful self-administration after reading simple product instructions.

Results. We successfully formulated and optimized MAP projection geometry to accommodate high drug-loading requirements of CAB LA (5.86 mg CAB LA per 1 cm^2 MAP), a hydrophobic drug. The MAPs are stable for 6 months under accelerated aging conditions in foil packaging, readily pierce the skin, and rapidly dissolve. In rats, plasma concentration levels of CAB LA were maintained above therapeutic targets of 4xPA-IC90 for 28 days; however, bioavailability was lower than IM or ID injection controls. Photos: QUB. MAPs dissolving over time in phosphate-buffered solution; MAP projections fully dissolved within 25 minutes.

Conclusion. Additional development work is warranted, including optimizing bioavailability, evaluating MAPs as a maintenance dose in vivo, conducting cost of manufacturing and cost of delivery analyses, and assessing potential end-user acceptability.





Disclosures. Bill Spreen, PharmD, ViiV Healthcare (Employee), Trevor Scott, RPh, PhD, ViiV Healthcare (Employee). **Others Authors:** No reported disclosures.

LB9. The Effect of Initiating Integrase Inhibitor-based vs. Non-Nucleoside Reverse Transcriptase Inhibitor-based Antiretroviral Therapy on Progression to Diabetes among North American Persons in HIV Care

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Session: 184. Late Breaker Oral Abstract Session 2
Friday, October 4, 2019: 1:55 PM

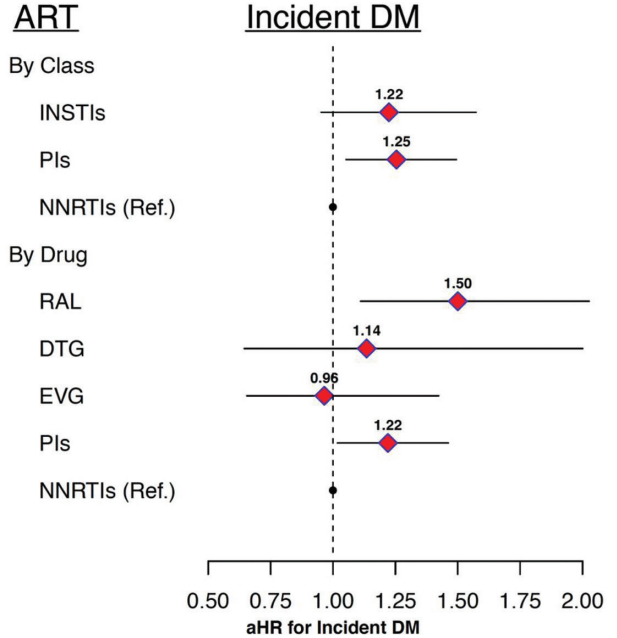
Background. Integrase strand transfer inhibitor (INSTI)-based antiretroviral therapy (ART) has been implicated in greater weight gain than other regimens among people with HIV, but there is little evidence about its role in serious clinical outcomes proximal to weight gain. We therefore examined the impact of initial ART regimen class/drug on incident diabetes mellitus (DM) in a large North American HIV cohort.

Methods. Treatment-naïve adults (≥18 years) initiating INSTI-, protease inhibitor (PI)-, or non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART from January 2007 to December 2016 in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) were included. Individuals were followed until date of incident DM (HgA1c >6.5%, diabetes-specific medication, DM diagnosis along with diabetes-related medication, or random glucose measure ≥200 mg/dL), virologic failure, regimen core switch, cohort close (through December 2016), death date, or loss to follow-up (≥12 months with no contact before cohort close). Cox regression stratified by site and adjusting for age, sex, race, HIV transmission risk, year of ART initiation, and baseline weight, $CD4^+$ cell count, and HIV-1 RNA yielded adjusted hazard ratios (HR) and 95% confidence intervals (CI) for incident DM by ART class and INSTI drug.

Results. Among 21,516 eligible ART initiators, 10,553 (49%) started NNRTIs, 6,677 (31%) PIs, and 4,286 (20%) INSTIs, with median follow-up of 3.0, 2.4, and 1.6 years, respectively. Among INSTI initiators, 21% started dolutegravir (DTG), 28% raltegravir (RAL), and 51% elvitegravir (EVG). Overall, 669 (3%) developed DM. Patients differed by all characteristics except baseline body mass index and HIV-1 RNA. Those starting INSTIs vs. NNRTIs had increased risk of incident DM (HR = 1.22; CI: 0.95–1.57) similar in magnitude as for PI vs. NNRTI initiators (HR = 1.25; CI: 1.05–1.49) (figure). Among INSTIs, starting RAL- vs. NNRTI-based ART was associated with a 50% increased risk of DM (HR = 1.50, CI: 1.11–2.03).

Conclusion. Initiating ART with INSTI- or PI- vs. NNRTI-based regimens may confer increased risk of incident DM, though risk is heterogeneous among INSTIs. Further research is needed to determine whether this elevated risk can be attributed to weight gain.

Figure. Adjusted hazard ratios (aHR) and 95% confidence intervals for the association between antiretroviral therapy (ART) regimen classes and drugs and incident diabetes mellitus (DM).



- INSTI: integrase strand transfer inhibitor; PI: protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; RAL: raltegravir; DTG: dolutegravir; EVG: elvitegravir
- Continuous covariates were modeled using restricted cubic splines with 5 knots to relax linearity assumptions, missing data were multiply imputed, and Cox models were stratified by site.

Disclosures. Kassem Bourgi, MD, Gilead Sciences (Grant/Research Support), Joseph J. Eron, MD, Gilead Sciences (Consultant, Grant/Research Support), Janssen (Grant/Research Support), Merck (Consultant), ViiV Healthcare (Consultant, Grant/Research Support), M. John Gill, MB, ChB, MSc, Gilead (Board Member), Merck (Board Member), Viiv (Board Member), Michael Silverberg, PhD, MPH, Gilead (Grant/Research Support). **Other Authors:** No reported disclosures.

LB10. A Randomized, Double-Blind, Placebo-Controlled Efficacy Trial of a Vaccine to Prevent Chronic Hepatitis C Virus Infection in an at-Risk Population

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Session: 184. Late Breaker Oral Abstract Session 2
Friday, October 4, 2019: 2:05 PM

Background. The development of a safe and effective vaccine to prevent chronic hepatitis C virus (HCV) infection is a critical component of elimination efforts, providing the rationale for the first HCV vaccine efficacy trial.

Methods. In a randomized, multicenter, double-blind, placebo-controlled efficacy trial (NCT01436357), we evaluated a recombinant chimpanzee adenovirus 3 vector vaccine prime followed by a recombinant modified vaccinia Ankara boost, both encoding nonstructural proteins of HCV. HCV-uninfected adults 18–45 years old at-risk for HCV infection due to injection drug use were randomized to receive the prime-boost regimen or placebo at Days 0 and 56. Trial participants were monitored for vaccine reactogenicity, adverse events, and HCV viremia. Vaccine safety, immunogenicity, and efficacy against progression to chronic HCV infection were assessed.

Results. A total of 455 subjects received the prime-boost regimen or two doses of placebo, with 202 and 199 in the respective groups included in the according-to-protocol efficacy cohort. Overall incidence of infection was 14.1 infections per 100 person-years. There were no differences in development of chronic infection between vaccine and placebo arms, with 14 chronically infected subjects in each group. Specifically, the vaccine efficacy in preventing chronic infection was −0.53 (95% confidence interval [CI], −2.5 to 0.34). Of vaccinated subjects, 78% generated T-cell responses to ≥1 vaccine-encoded HCV antigens. The vaccine was generally safe and well tolerated with no serious vaccine-related adverse events. There were more solicited reports of adverse events after either injection in the vaccine group (81%) than in the placebo group (59%), with the difference mainly due to injection-site reactions. Serious adverse events and deaths occurred with similar frequencies in the two groups.

Conclusion. A randomized, placebo controlled, Phase I/II trial of a prime-boost vaccine to prevent chronic HCV infection was completed in an at-risk population, demonstrating the feasibility of conducting rigorous vaccine research in people who inject drugs. The regimen elicited robust immune responses without evident safety concerns, but did not provide protection against chronic HCV infection.

Disclosures. Ventzislav Vassilev, PhD, GlaxoSmithKlein Vaccines (Employee), Lan Lin, MD, GlaxoSmithKlein Vaccines (Employee), Alfredo Nicosia, PhD, ReiThera (Employee, Shareholder), Antonella Folgori, PhD, ReiThera (Employee), ReiThera (Employee, Shareholder. **Other Authors:** No reported disclosures.

LB11. A Single Dose of the MVA-BN Smallpox Vaccine Induces an Early Protective Antibody Response Similar to a Traditional Replicating Vaccine and Is Suitable for Emergency Scenarios

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Session: 184. Late Breaker Oral Abstract Session 2
Friday, October 4, 2019: 2:15 PM

Background. Smallpox remains a high-priority threat due to its potential for re-emergence through events including bioterrorism and spontaneous mutation. While traditional replicating smallpox vaccines such as ACAM2000 are associated with serious side effects, the non-replicating MVA BN smallpox vaccine was developed as a safer alternative.

Methods. This phase 3 non-inferiority study compared indicators of efficacy between the MVA-BN smallpox vaccine and ACAM2000. The co-primary endpoints were (1) to compare vaccine-induced serum neutralizing antibodies (geometric mean titer [GMT]) at predefined Peak Visits, as measured by plaque reduction neutralization tests (PRNT) and (2) to assess the attenuation of ACAM2000-induced takes after MVA-BN administration by measuring maximum lesion area (MLA). Early neutralizing antibody GMTs at Day 14, a timepoint considered protective for traditional replicating smallpox vaccines, were also compared following single doses of either vaccine.

Results. A total of 440 subjects were evenly randomized to receive either 2 doses of MVA-BN followed by 1 dose of ACAM2000 at 4 week intervals (Group 1) or a single dose