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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**

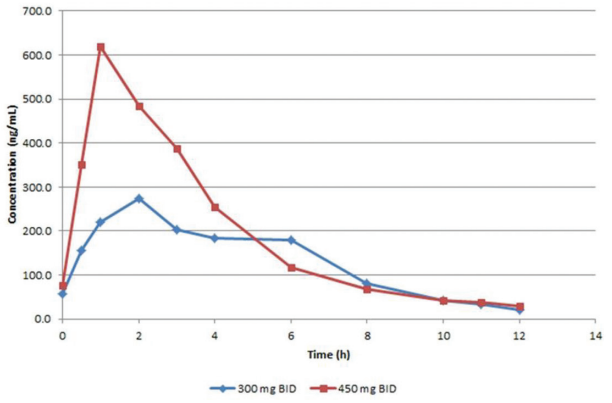
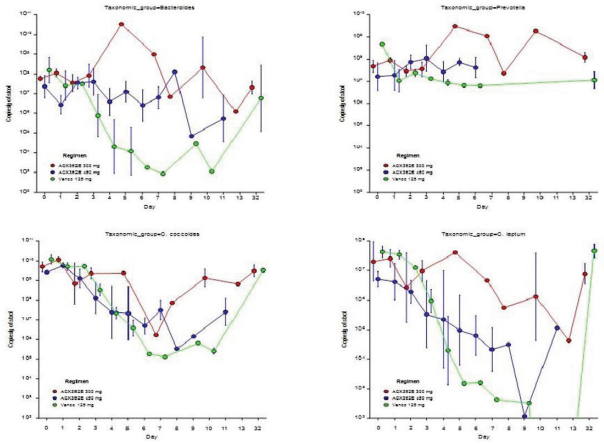


Figure 2. Microbiota levels belonging to different taxonomic groups measured by qPCR in samples



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

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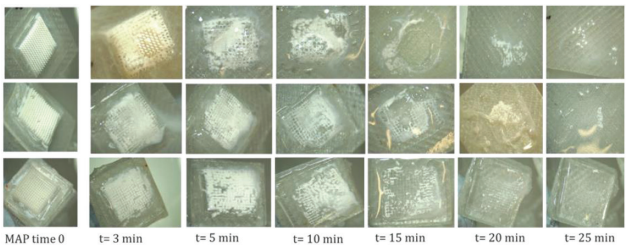
Session: 184. Late Breaker Oral Abstract Session 2
Friday, October 4, 2019: 1:45 PM

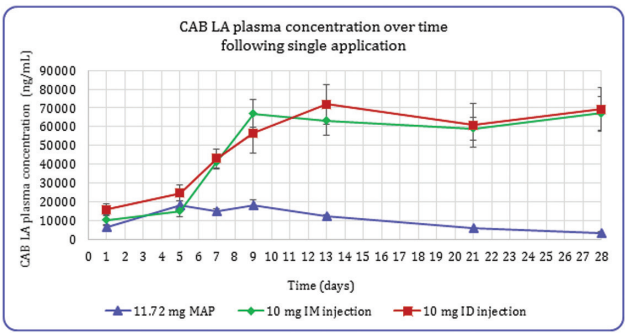
Background. The purpose of this research was to develop a microarray patch (MAP; also known as a microneedle patch) for delivery of long-acting cabotegravir (CAB LA) for HIV pre-exposure prophylaxis (PrEP) and co-delivery of long-acting CAB LA and a hormonal contraceptive to enable a future multi-purpose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