First of a New Class of Antibiotics (DNA pol IIIC Inhibitors) Targeting CDC/FDA/WHO Priority Pathogens

Preparing for the Next Pandemic: Antimicrobial Resistance in Gram-positive Bacterial Infections

Presenters:

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ACURX PHARMACEUTICALS, INC.

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* *Dr. Silverman is an independent consultant to Acurx: No disclosures; Dr. Garey has received research grants paid to his university from Acurx Pharmaceuticals, Paratek Pharmaceuticals, and Merck & Co; All relevant financial disclosures have been mitigated*

AMR: GLOBAL CHALLENGE

We must prepare our public health systems to fight multiple threats, simultaneously. Now is the time to address our current antimicrobial-resistant threats, while simultaneously preparing for unknown emerging threats in the future.*

Unmet Medical Need:
CDC/FDA classification:

- ***C. difficile*: urgent *XDR threat*** *requiring new antibiotic development;*
- ***MRSA, VRE, PRSP serious threats***

- *Clostridioides difficile (C. diff)*
- Drug-resistant *Neisseria gonorrhoeae*
- Drug-resistant *Campylobacter*
- Drug-resistant nontyphoidal *Salmonella*
- Drug-resistant *Salmonella* serotype Typhi
- Drug-resistant *Shigella*
- Drug-resistant *Streptococcus pneumoniae*
- Erythromycin-resistant group A *Streptococcus*
- Clindamycin-resistant group B *Streptococcus*

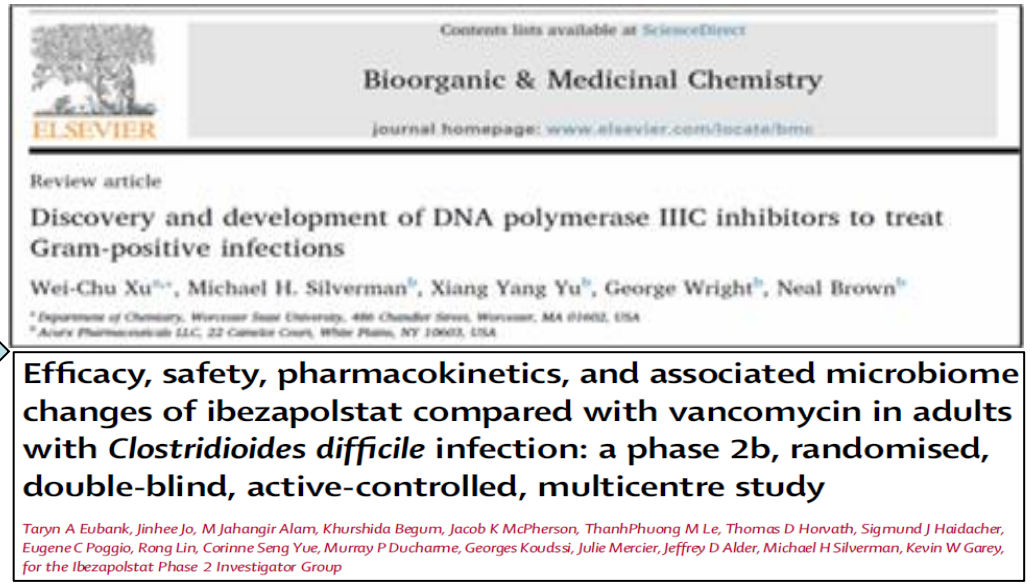
RE-EMPHASIZED PRIORITY PATHOGENS

- Carbapenem-resistant *Acinetobacter* (↑78%)
- Antifungal-resistant *Candida auris* (↑60%)*
- Carbapenem-resistant Enterobacterales (↑35%)
- Antifungal-resistant *Candida* (↑26%)
- ESBL-producing Enterobacterales (↑32%)
- Vancomycin-resistant Enterococcus (↑14%)
- Multidrug-resistant *P. aeruginosa* (↑32%)
- Methicillin-resistant *Staphylococcus aureus* (↓13%)

ACURX: COMPANY MISSION

- Develop new class of antibiotics for difficult-to-treat bacterial infections
- First of a new class of antimicrobials** addresses global crisis of AMR
- Previously unexploited bacterial target – DNA pol IIIC – critical for DNA replication of certain Gram-positive bacteria

ACCUMULATING DATA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Bioorganic & Medicinal Chemistry

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Review article

Discovery and development of DNA polymerase IIIC inhibitors to treat Gram-positive infections

Wei-Chu Xu, Michael H. Silverman, Xiang Yang Yu, George Wright, Neal Brown

Efficacy, safety, pharmacokinetics, and associated microbiome changes of ibezapolstat compared with vancomycin in adults with *Clostridioides difficile* infection: a phase 2b, randomised, double-blind, active-controlled, multicentre study

Taryn A Eubank, Jinhee Jo, M Jahangir Alam, Khurshida Begum, Jacob K McPherson, ThanhPhuong M Le, Thomas D Horvath, Sigmund J Haidacher, Eugene C Poggio, Rong Lin, Corinne Seng Yue, Murray P Ducharme, Georges Koudssi, Julie Mercier, Jeffrey D Alder, Michael H Silverman, Kevin W Garey, for the Ibezapolstat Phase 2 Investigator Group

Lancet Microbe. 2025 Aug;6(8):101126.

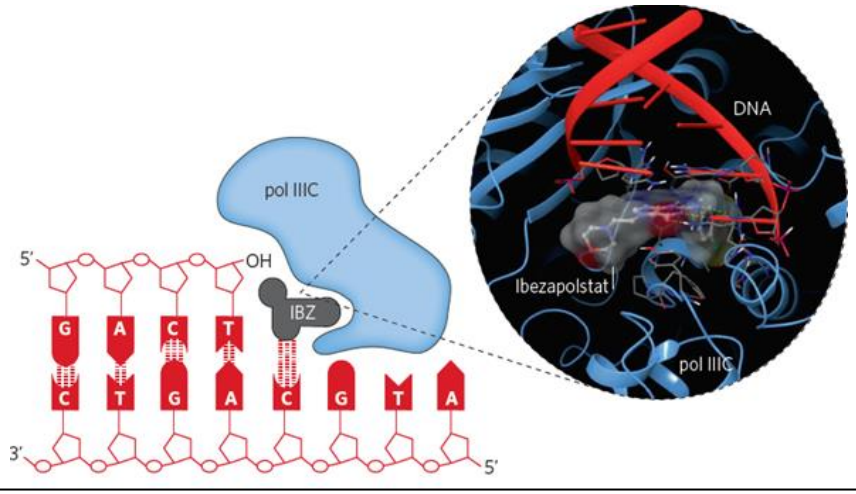
*Excerpted from: CDC. COVID-19: U.S. Impact on Antimicrobial Resistance, Special Report 2022. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2022. https://www.cdc.gov/drugresistance/covid19.html

**Patented to May 2032 with 10 years regulatory exclusivity from FDA approval (QIDP and NCE)

Acurx Platform Technology and Pipeline

DNA Polymerase IIIC Inhibition:

- Innovation criteria[1]:
  - ✓ New chemical class
  - ✓ New target
  - ✓ New MOA
  - ✓ No cross-resistance
- Gram-Positive Selective Spectrum (GPSS®) antibiotics target multi-drug-resistant bacterial pathogens (including *C. difficile*, MRSA, VRE, DRSP) – FDA QIDP/Fast Track designated/eligible for *C. difficile* Infection (CDI)



Compounds block the active site of the Gram+ specific bacterial enzyme DNA polymerase IIIC (pol IIIC), inhibiting DNA replication

Ibezapolstat (IBZ) Oral Phase 2 Trial:

- **Phase 2A (n = 10)[2]:**
  - Efficacy results = 100% Clinical Cure (CC) and Sustained Clinical Cure (SCC) (n=10) provide clinical validation for targeting pol IIIC to treat G+ pathogens
  - Microbiome restoration/sparing and bile acid ratio may inhibit recurrence
- **Phase 2B (n = 32)[3]:**
  - Randomized, blinded, vancomycin (VAN)-controlled
  - Efficacy results in the Per Protocol Population:
    - CC: 15/16 (93.8%) IBZ subjects vs 14/14 (100.0%)
    - SCC: 15/16 (93.8%) IBZ subjects vs 12/14 (85.7%) VAN subjects
  - Overall Phase 2 IBZ Per Protocol CC and SCC rates = 25/26 (96.2%); no recurrence
  - IBZ 450 mg BID was safe and well-tolerated
- **This first-in-class antibiotic is Phase 3 ready (both FDA and EMA)**
- **Commercial supply chain: Made in America**

[1]*Theuretzbacher, WHO, 2017;* [2]*Garey, CID, 2022;* [3]*Eubank, Lancet Microbe, 2025*

Factors Informing Ibezapolstat Registration Trials

- **Nonclinical:**
  - Bactericidal potency vs *C. difficile* (MIC_{90} = 4 µg/mL)
  - Potency maintained against MDR strains
  - Does not trigger sporulation or toxin release
  - Reduced flagellar movement; active in biofilms
  - Microbiome effects similar to FDX in humanized mouse model
- **Clinical:**
  - No Phase 2 SAEs or withdrawals due to AEs; treatment-related AEs were primarily mild GI events
  - 96.2% (25/26) Clinical Cure at End of Treatment in Phase 2
  - 96.2% (25/26) Sustained Clinical Cure at Day 38 in Phase 2
  - High human fecal concentrations (>1000x MIC)
  - Rapid eradication of *C. difficile* (by Day 3) in patients
  - Gut microbiome: Preservation of key Firmicutes species relative to VAN
  - Bile acids: Increase in secondary bile acids relative to VAN
- **IBZ is Phase 3 Ready:**
  - CDI Protocols IBZ-ASPIRE-1 and -2 for US NDA and EU MAA; NI vs VAN; n=474 ea

Objectives	Endpoints
Primary Efficacy	
Evaluate the efficacy of ibezapolstat and vancomycin determined by the incidence of Clinical Cure (CC) in the treatment of C. difficile infection (CDI)	CC at the Test of Cure (TOC) visit (Day 12)
Primary Safety	
Evaluate the safety and tolerability of ibezapolstat administered every 12 hours for 10 days in the treatment of CDI	Type, frequency, and severity of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs)
Secondary Efficacy	
Evaluate incidence of Sustained Clinical Cure (SCC)	SCC at 28 ±2 days after EOT (Day 38)

Systemic GPSS® Antibiotic Platform

- **Systemic DNA Pol IIIC Inhibitor Platform**: Systemic treatment of *Staphylococcus, Streptococcus and Enterococcal* infections, including MRSA, VRE, and other resistant G+ bacterial infections; WHO/CDC Priority Pathogen Lists[1]
  - Novel bactericidal mechanism of action, inhibiting DNA pol IIIC, present in G+ but not in G- bacteria or mammals[2]
  - Bacteria resistant to current antibiotics, including daptomycin, telavancin, ceftaroline, new tetracyclines & linezolid-resistant bacteria
  - In hospitalized patients in the United States, MRSA accounted for 52% of all infections, almost twice as many as MDR Gram-negative infections[3]
  - VRE hospital infections exceeded carbapenem-resistant (CR) Acinetobacter, MDR *Pseudomonas aeruginosa,* and CR Enterobacteriaceae infections combined[3]

- **Potential Clinical Indications for Oral and IV Delivery**:
  - Acute bacterial skin and skin-structure infections (including those caused by MRSA)
  - Community-acquired bacterial pneumonia, hospital and/or ventilator-associated bacterial pneumonia; anthrax
  - Bacteremia with or w/o sepsis and/or infectious endocarditis; bone/joint infections & diabetic foot infections

[1] CDC Antibiotic Resistance Threats in the U.S., 2019, Atlanta, U.S. Department of Health and Human Services, CDC, Nov. 2019; [2] Xu, et al., Bioorganic & Medicinal Chemistry https://doi.org/10.1016/j.bmc.2019.06.017; [3]Jernigan, et al., Multidrug-Resistant Bacterial Infections in U.S. Hospitalized Patients, 2012–2017, *N Engl J Med* 382:1309-19; (2020)

Systemic GPSS® Antibiotic Program Status

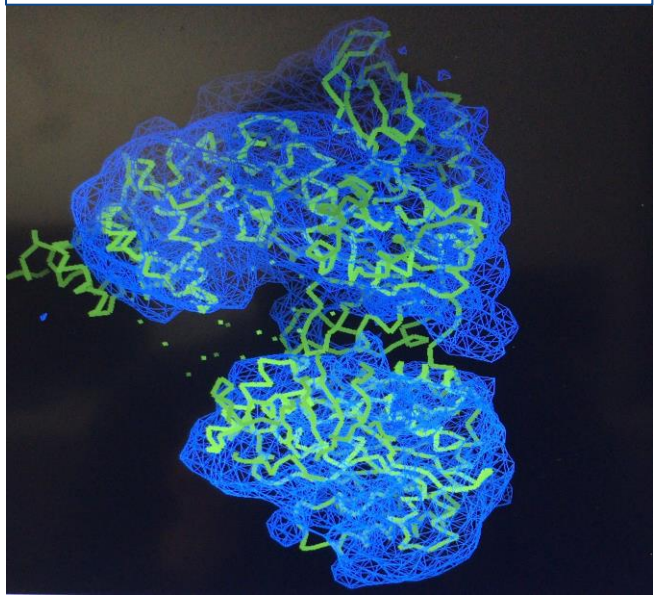
Hit-to-Lead testing of >600 novel compounds has resulted in significant advances of drug-like properties:

- In vitro & in vivo safety
- Oral and IV efficacy in mouse infection models including in neutropenic mice (MRSA systemic & thigh, VRE thigh, and PRSP lung)

Lead Optimization:

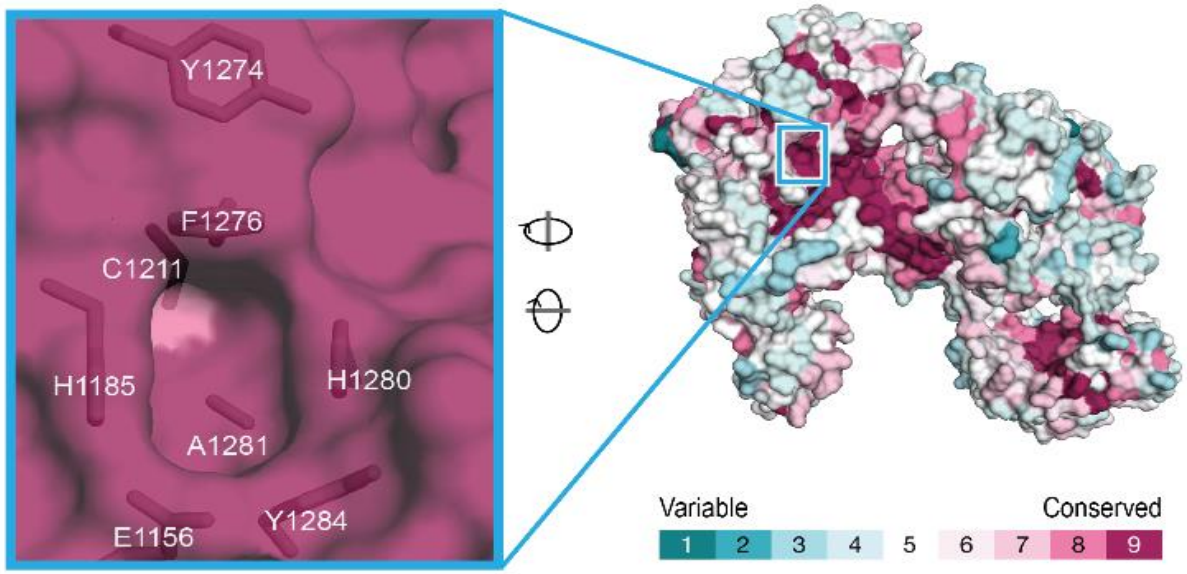
- ***Current priority: development of oral antibiotic for MRSA/MSSA in ABSSSI to speed advance into clinic***
  - ***Potential for development as a biothreat treatment (B. anthracis) piggybacking on the ABSSSI/pneumonia program with use of Animal Rule for anthrax approval***
- Advanced molecular modeling based on improved leads
- Collaboration with Leiden University Medical Center:
  - High-throughput measurement of pol IIIC inhibition
  - 3D structure elucidation of pol IIIC enzyme alone and bound to Acurx inhibitors
  - Design of new compounds based on 3D target binding site data

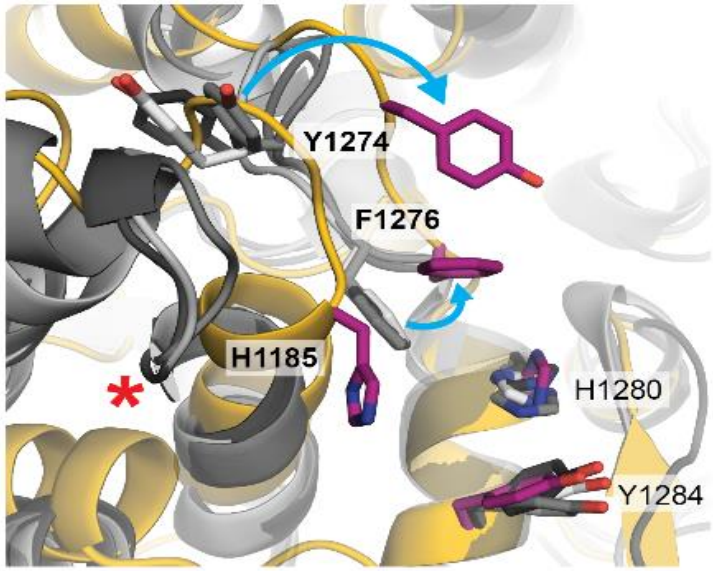
Early 3D Image Map: VRE Pol IIIC



Structural Biology of DNA pol IIIC Inhibition

Nature Communications IN-PRESS: *A unique inhibitor conformation selectively targets the DNA polymerase PolC of Gram-positive priority pathogens (Smits*, Leiden University Medical Center)*





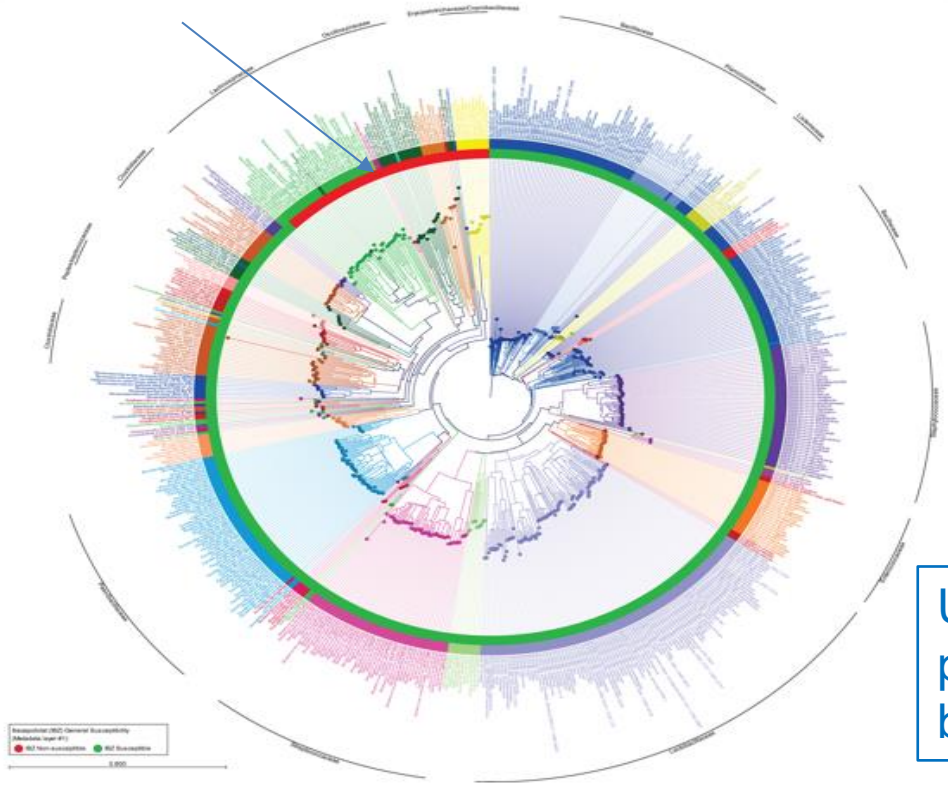
▪ Structural biology using cryo-electron microscopy ▪ Resolution of 2.8 Angstrom ▪ First PolC structure with DNA and inhibitor bound	▪ Mechanistic insights into MOA ▪ Structural explanation for selective spectrum ▪ Mechanism conserved in Gram- positive priority pathogens

*Corresponding author: Wiep Klaas Smits, PhD; Associate Professor /Principal Investigator for Pol C Inhibitors, Leiden University Medical Center

Cladographic Explanation of Ibezapolstat Selectivity

February 24, 2025; AAC: *The Microbiome-restorative Potential of Ibezapolstat for the Treatment of Clostridioides difficile Infection is Predicted Through Variant PolC-type DNA Polymerase III in Lachnospiraceae and Oscillospiraceae* (McPherson et al, AAC 2025)*

Inner red line = IBZ resistant isolates (Clostridiales)



- In silico evaluation of gut bacterial DNA pol IIIC phylogeny
- Cladogram shows variations in enzyme structure that account for IBZ selective activity in the gut and sparing of beneficial (bile acid metabolizing) gut flora

Unique genomic changes within these phylogeny differ from other Gram-positive bacterial DNA pol IIIC including *C. difficile*

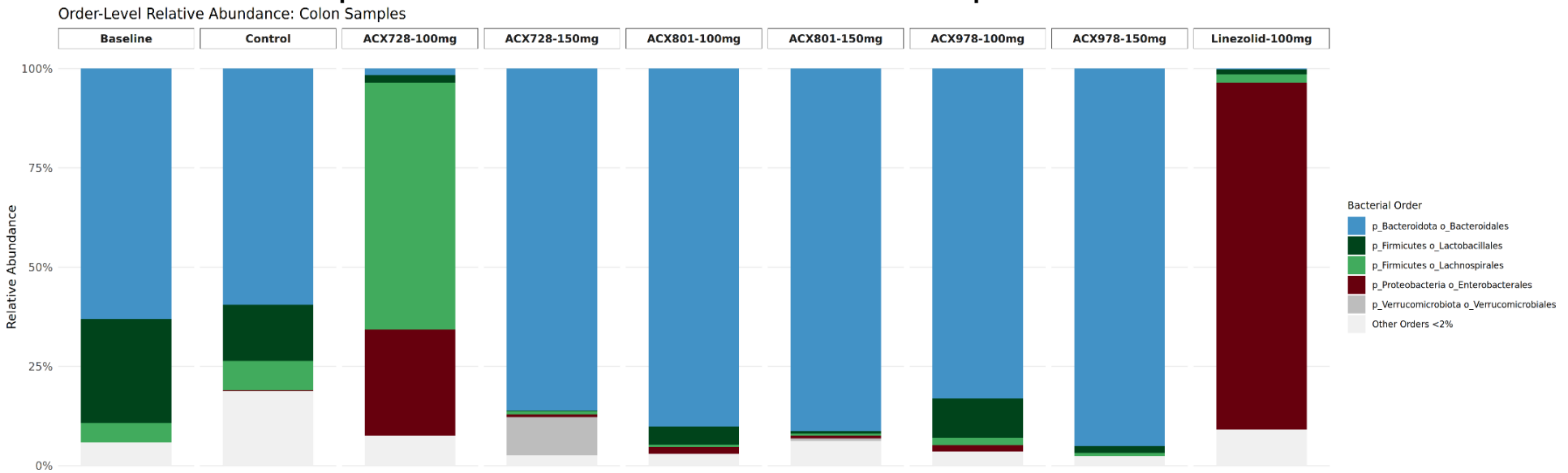
Co-author Dr. Kevin Garey: Commented on the results stating: "These studies help to explain the narrower than expected spectrum of activity of ibezapolstat in our ongoing clinical trials that helps explain regrowth of beneficial gut microbiota while patients are on ibezapolstat therapy. Genomic differences in the PolC between these species affect the binding of ibezapolstat allowing these beneficial microbes to be resistant and confer health benefits. This is distinctly different that the comparator vancomycin which kills these beneficial microbes causing high rates of *C. difficile* recurrence." **Acurx Press Release, 24 February 2024

*Co-author: Kevin Garey, PharmD, MS, FIDSA, Professor and Chair, University of Houston College of Pharmacy, Principal Investigator for microbiology and microbiome aspects of the IBZ clinical trial program, Acurx Scientific Advisory Board Member

Microbiome Selectivity in Other DNA Pol IIIC inhibitors

NEW DATA

MRSA thigh infection model in neutropenic mice (4 mice per group). Microbiome analysis from colon sections. Three representative DNA pol IIIC inhibitor compounds in preclinical development were tested at two doses compared to linezolid.



These experiments provide initial evidence that the microbiome selectivity of IBZ **may be a class effect for pol IIIC inhibitors**.

- Mice had high abundance of Bacteroidales at baseline (beneficial gut flora, pol IIIC-negative)
- Bacteroidales increased in abundance for almost all pol IIIC inhibitor compounds
- One low-dose pol IIIC-inhibitor compound increased abundance of pol IIIC-positive beneficial gut flora
- Enterobacterales increased in abundance in linezolid-treated mice

*Co-author: Kevin Garey, PharmD, MS, FIDSA, Professor and Chair, University of Houston College of Pharmacy, Principal Investigator for microbiology and microbiome aspects of the IBZ clinical trial program, Acurx Scientific Advisory Board Member

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Targeting CDC/FDA/WHO Priority Pathogens

Preparing for the Next Pandemic: Antimicrobial Resistance in Gram-positive Bacterial Infections

For additional information and/or to express interest in participating as an investigator in our IBZ Ph3 clinical trials,
please visit our booth #215 or capture the QR code here

THANK YOU!

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