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

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

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IDWeek, October 12, 2023
New Antimicrobials in the Pipeline

Robert J. DeLuccia, Executive Chairman

ACURX PHARMACEUTICALS, INC.

* *Dr. Silverman is an independent consultant to Acurx; No disclosures*

Disclosure

Acurx

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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.*

- *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*

Unmet Medical Need:
CDC/FDA classification:

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

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
- Lead DNA pol IIIC Inhibitor discovered by Wright/Brown, Professors Emeriti, UMass;
- 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


Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Review article

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

Wei-Chu Xu[a,*], Michael H. Silverman[b], Xiang Yang Yu[b], George Wright[b], Neal Brown[b]


> Clin Infect Dis. 2022 Feb 4;ciac096. doi: 10.1093/cid/ciac096. Online ahead of print.

Efficacy, Safety, Pharmacokinetics, and Microbiome Changes of Ibezapolstat in Adults with Clostridioides difficile Infection: A Phase 2a Multicenter Clinical Trial

Kevin W Garey [1 2], Jacob McPherson [1], An Q Dinh [2], Chenlin Hu [1], Jinhee Jo [1], Weiqun Wang [1], Chris K Lancaster [1], Anne J Gonzales-Luna [1], Caroline Loveall [1], Khurshida Begum [1], M Jahangir Alam [1], Michael H Silverman [3], Blake Hanson [2]

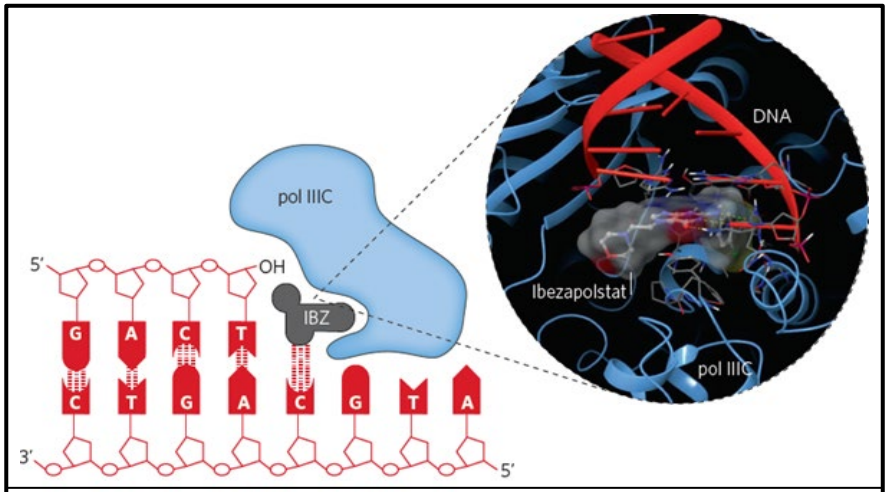
*Excerpted from: CDC. COVID-19: U.S. Impact on Antimicrobial Resistance, Special Report 2022. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2022. https://www.cdc.gov/drugresistance/covid19.html

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

Acurx 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 all low G + C bacterial pathogens (including *C. difficile*, MRSA, VRE, DRSP) – FDA QIDP/Fast Track designated/eligible
- Ibezapolstat (oral) potential for first-line treatment of *C. difficile* Infection



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

Ibezapolstat Phase 2:

- **Phase 2a:** efficacy results = 100% Clinical Cure and Sustained Cure (n=10)(*CID, 2022*) provide clinical validation for targeting pol IIIC
  - Microbiome restoration/sparing and bile acid ratio may inhibit recurrence[2]
- **Phase 2b:**
  - Randomized, blinded, vancomycin-controlled; n=32 successful completion and early discontinuation
  - Based on observed aggregate blinded data both treatment performed as expected
  - High rate of Clinical Cure (Primary Efficacy endpoint) observed without any emerging safety concerns
  - Data will be analyzed and topline efficacy results will be reported as soon as possible
  - Successful milestone will allow advancement of this first-in-class antibiotic candidate to Ph3 clinical trials more expeditiously

[1]*Theuretzbacher, WHO, 2017;* [2]*Garey ,CID, 2022*

Systemic GPSS™ Antibiotic: Program Highlights

- **Systemic Pol IIIC Inhibitor Program**: 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 Products**:
  - Acute bacterial skin and skin-structure infections (including those caused by MRSA)
  - Community-acquired bacterial pneumonia, hospital and/or ventilator-associated bacterial pneumonia; bacteremia with or w/o 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

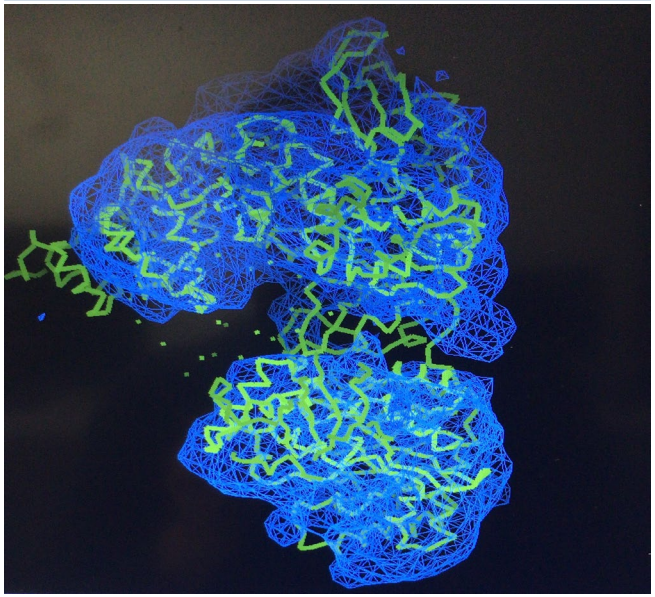
Hit-to-Lead testing of >500 novel compounds has resulted in significant advances:

- 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: Improve drug-like properties:

- 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
- Prodrug approaches for both oral & IV delivery
- ***Current priority: development of oral antibiotic for MRSA/MSSA in ABSSSI to speed advance into clinic***

Early 3D Image Map: VRE Pol IIIC

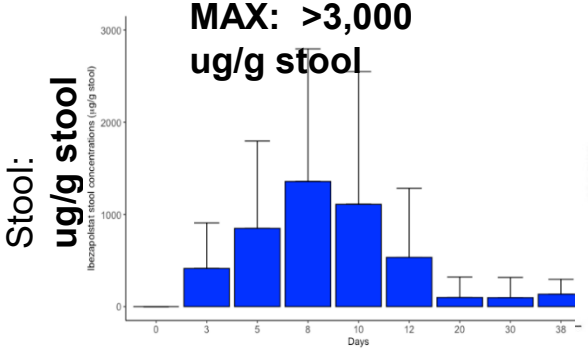


Ibezapolstat: Investigating *C. difficile* Efficacy and Anti-recurrence Properties

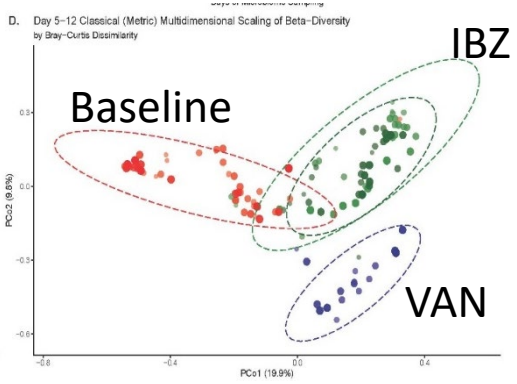
Clinical development program included a new method to assess for anti-recurrence properties

Phase I study: Healthy volunteers

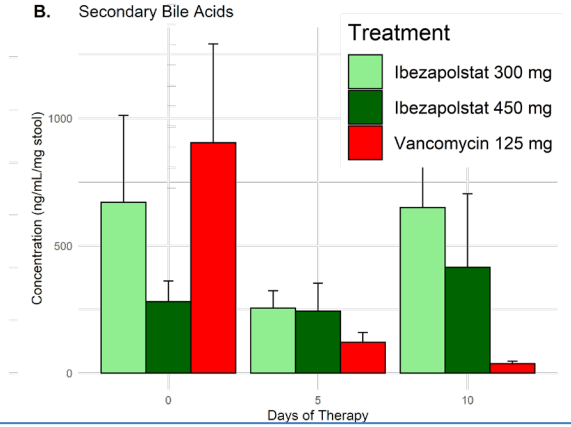
High Stool Concentrations



Microbiome changes distinct from vancomycin

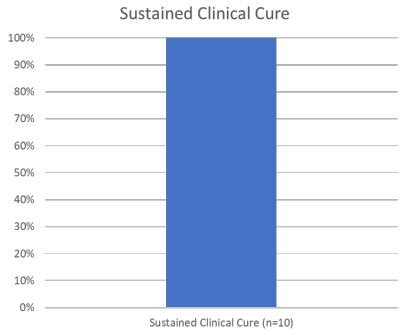


Preservation of secondary bile acids

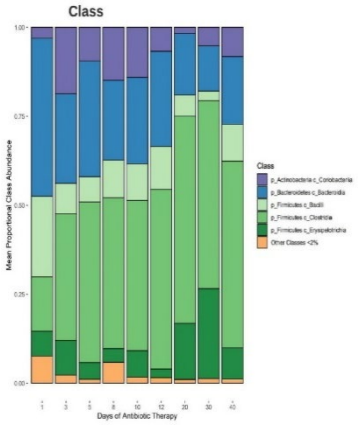


Phase 2a study: 10 patients with confirmed *C. difficile* infection

100% sustained clinical cure with no recurrence

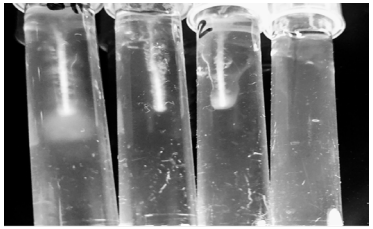


Preservation of microbial taxa known to metabolize primary bile acids

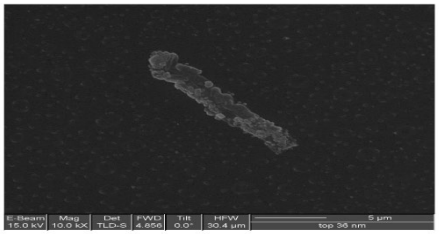


Ibezapolstat: Anti-virulence, Microbiome and MDRO properties

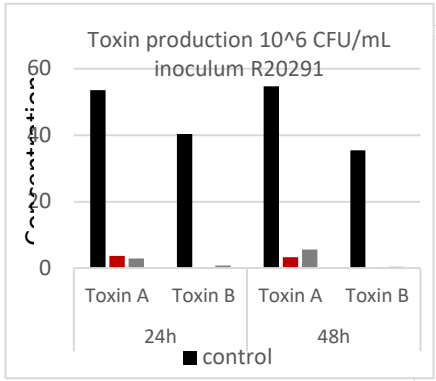
REDUCED FLAGELLA MOVEMENT[1] in concert with reduced expression of primary genes used to synthesize flagella



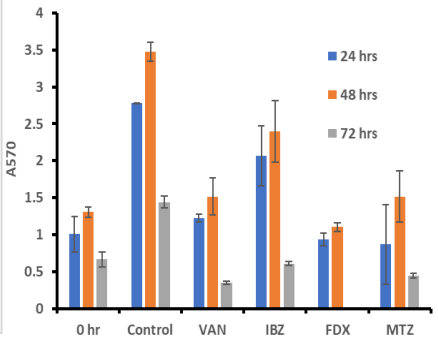
EFFECTIVE AGAINST MDRO STRAINS[1]**:** *C. difficile* strains with reduced susceptibility to MET, VAN, FDX were susceptible to ibezapolstat



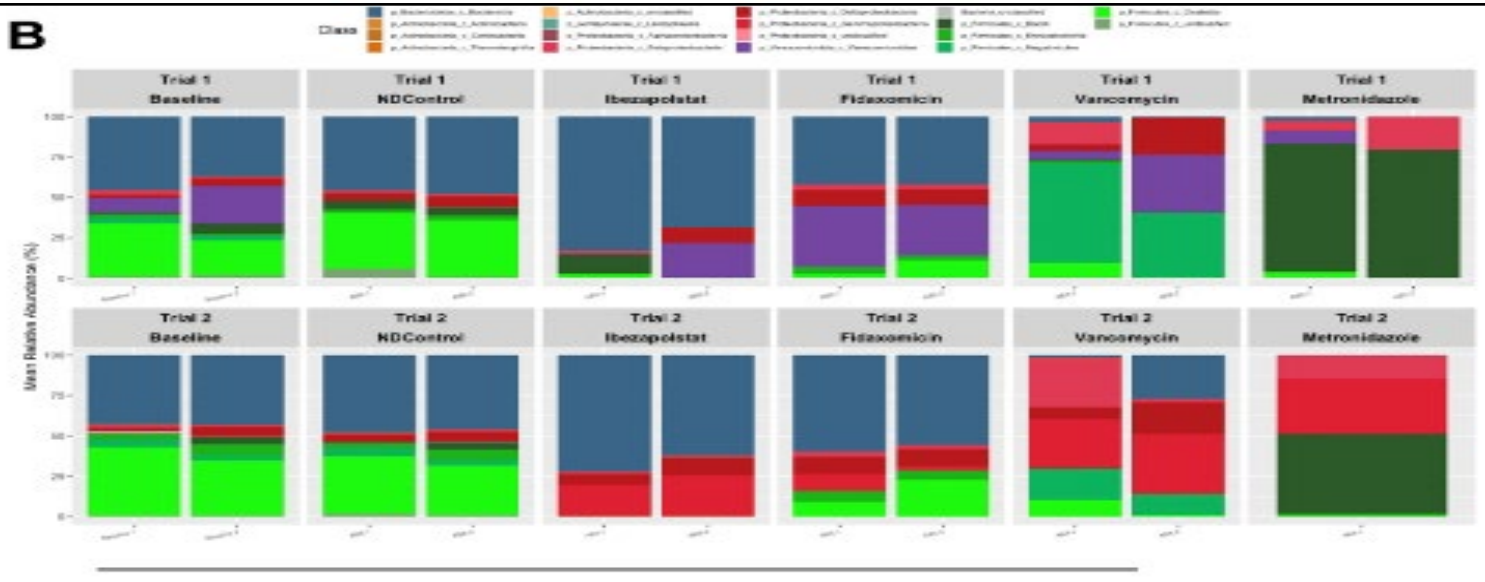
REDUCED TOXIN PRODUCTION[2]



EFFECTIVE *C. difficile* KILLING IN BIOFILMS[3]



HUMANIZED MOUSE MODEL[4]
Microbiome disruption similar to fidaxomicin
VAN &MET>>>
IBZ & FDX



[1]Basseres et al, ECCMID, 2023; Bassères et al. [2]Anaerobe 2022 poster # PII-25; Bassères et al. [3]ECCMID 2023 poster #3422/P2144; Bassères et al. Clostpath 2023 poster #121; [4]Jo et al. Clostpath 2023 poster #79

Promising Signals for Ibezapolstat

Factors that provide confidence in successful outcomes of future clinical trials:

- **Nonclinical**
  - Bactericidal potency vs *C. difficile*
  - Effective against MDR strains
  - Does not trigger sporulation or toxin release
  - Reduced flagellar movement
  - Active in biofilms
  - Microbiome disruption similar to FDX in humanized mouse model
- **Clinical**
  - Excellent human safety profile
  - 100% Clinical Cure at EOT in Ph2a (n=10)
  - 100% Sustained Cure at Ph2a follow up
  - High human fecal concentrations (>1000x MIC)
  - Rapid eradication of *C. difficile* (by Day 3) in patients
  - Favorable microbiome effects by day 3 while on treatment
  - Favorable effect on bile acids
  - High aggregate Clinical Cure rate in Ph2b (n=32)

Ibezapolstat: *Killing the Bug but Sparing the Microbiome*

- Evaluation of potential anti-recurrence properties earlier in clinical trials could become the new standard for anti-*C. difficile* drug development
- Knowledge of novel MOA (DNA inhibitor) led to testable hypotheses of anti-virulence properties and effectiveness against MDR strains
- Nonclinical pharmacology and clinical results support the continued development of ibezapolstat for treatment of CDI
- Ibezapolstat activity validates DNA pol IIIC as a clinical target
- Features of ibezapolstat pharmacology, including gut microbiome-sparing in patients with CDI; may be a class effect of DNA pol IIIC inhibitors