Acurx Pharmaceuticals
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Advancing a promising antibacterial against *Clostridioides difficile*

Acurx Pharmaceuticals' first-in-class antibiotic ibezapolstat shows efficacy against *Clostridioides difficile* infection while sparing the microbiome.

Decades-old antibacterial drugs and growing drug resistance have significantly weakened the ability to effectively treat many bacterial infections. Despite this widely recognized threat to public health, investment in antibacterial drug development has lagged, with no new chemical class advancing to the clinic in decades. Acurx Pharmaceuticals, founded and led by veterans in the field, has broken this logjam, bringing a first-in-class antibacterial, ibezapolstat, into the clinic to treat *Clostridioides difficile* infection (CDI). An inhibitor of bacterial DNA polymerase IIIC (pol IIIC), ibezapolstat (Fig. 1) was well tolerated in a phase 1 study and recently shown to be effective in patients with CDI.

According to Bob DeLuccia, executive chairman at Acurx, "Data from our phase 2a trial in CDI patients show ibezapolstat not only has antibacterial activity against *C. difficile* but also spares other Gram-positive species essential for a healthy microbiome, lessening the chance of CDI recurrence." He continued, "This dual effect of eradicating *C. difficile* while at the same time providing a restorative effect on the microbiome has the potential to position ibezapolstat as a first-line therapy for CDI." Acurx also has another pol IIIC inhibitor program in its pipeline to treat systemic multidrug-resistant, Gram-positive infections, another area of high unmet need. The company recently went public, raising more than $17 million to support further clinical development and discovery.

Although *C. difficile* is part of the normal gut microbiome, CDI is a significant problem in hospitals and long-term care facilities, causing more than 500,000 infections and 20,000 deaths in the USA in 2020. Owing to this heavy toll on health, new drugs targeting *C. difficile* are covered under the Generating Antibiotic Incentives Now (GAIN) Act, an incentive program to encourage the development of new antibacterial drugs targeting high-priority pathogens. Ibezapolstat received US Food and Drug Administration (FDA) designation as a Qualified Infectious Disease Product and has received FDA priority review and fast-track status.

Groundbreaking clinical study

CDI, though localized exclusively in the gut, is difficult to treat, and patients receiving current standard-of-care therapy have a recurrence rate of 20–40%. This high recurrence rate is due, at least in part, to disruption of the microbiome and bile acid homeostasis by currently used antibacterials. In a groundbreaking genomic study conducted in collaboration with Kevin Garey at the University of Houston, effects of ibezapolstat on the microbiome of healthy volunteers were assessed and compared to those of vancomycin. The study found that ibezapolstat, but not vancomycin, spares critical Actinobacteria needed to restore a healthy intestinal microbiome. In addition, ibezapolstat appears to maintain a microbiome profile favorable to bile acid metabolism that may prevent quiescent *C. difficile* spores from germinating into live bacteria and initiating a new round of infection.

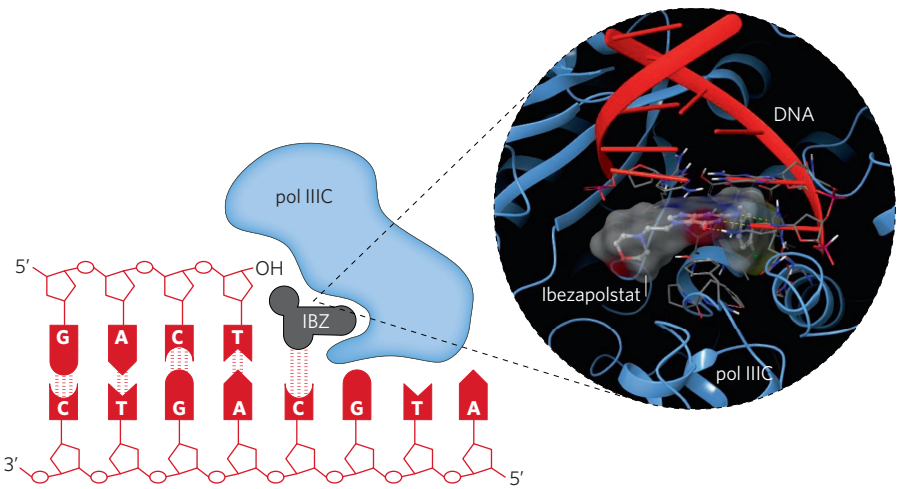

Fig. 1 | Ibezapolstat, a first-in-class antibacterial drug. Ibezapolstat (IBZ) is currently in a phase 2 trial against *Clostridioides difficile* infection, and inhibits bacterial DNA polymerase IIIC (pol IIIC) by interfering with addition of guanine (G) to the growing DNA chain.

The importance of this microbiome-preserving effect in avoiding CDI recurrence is supported by recent results of a phase 2a trial in patients with CDI, in which all ten patients treated with ibezapolstat orally twice daily for 10 days were cured, and clinical cure was sustained through day 38. These data were presented during IDWeek 2021 and begin to validate ibezapolstat's favorable microbiome effects, which may be predictive of beneficial patient outcomes, including low rates of recurrence. As president and CEO of Acurx, Dave Luci suggests, "If this trend is confirmed in later-stage trials, our scientific advisors believe ibezapolstat's gentler effect on the microbiome is likely to significantly reduce CDI recurrence and, if approved, would dramatically improve patient outcomes and reduce health-care costs." The company has filed a patent based on these findings. A phase 2b double-blind study comparing ibezapolstat with vancomycin in the same CDI patient population is scheduled to begin enrollment in 4Q 2021.

Acurx's ACX-375C preclinical program for systemic infections shares the same novel DNA pol IIIC-targeted mechanism of action and chemical scaffold as ibezapolstat and targets all known resistant and sensitive Gram-positive infections, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant Enterococci (VRE).

Progress through partnering

Acurx's scientific collaborators include WuXi AppTec, using the company's expertise for medicinal chemistry, biology and pharmacology to develop the structure-activity relationships and expand its pipeline of DNA pol IIIC inhibitors; and the Leiden University Medical Center to generate 3D crystal structures of DNA polymerases and their binding interactions with Acurx inhibitors, which should further speed discovery of new clinical candidates. Acurx is a member company of the Antimicrobials Working Group, the efforts of which bring the voice of biopharma to policymakers to help advance the field.

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