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Acurx Pharmaceuticals

Acurx Announces Publication of Nonclinical In Vivo Data Differentiating Ibezapolstat's Gut Microbiome Effects from Other Anti-CDI Antibiotics

- *First ever head-to-head comparison of gut microbiome changes associated with ibezapolstat (IBZ) to other anti-CDI antibiotics in a germ-free mouse model*
- *Changes in alpha and beta microbiome diversities following IBZ treatment were less pronounced compared to those observed in vancomycin (VAN)-or metronidazole (MET)-treated groups, complementing prior Phase 2 clinical findings showing IBZ's more selective antibacterial activity*
- *Notable differences were observed between the microbiome of IBZ- and fidaxomicin (FDX)-treated groups, which may allow for differentiation of these two anti-CDI antibiotics in future studies*
- *Results establish IBZ differentiating effects on the gut microbiome, indicating a more selective spectrum of microbiome alteration compared to broader-spectrum antibiotics like VAN and MET and a narrower spectrum of microbiome alteration compared to FDX*
- *Preparation continues to advance IBZ into international Ph3 clinical trials for treatment of CDI*
- *IBZ has previously been granted FDA QIDP and Fast-Track Designation and has received SME (Small and Medium-sized Enterprise) designation by the EMA*

STATEN ISLAND, N.Y., March 3, 2025 /PRNewswire/ -- Acurx Pharmaceuticals, Inc. (NASDAQ: ACXP) ("Acurx" or the "Company") is a late-stage biopharmaceutical company developing a new class of small molecule antibiotics for difficult-to-treat bacterial infections, with its lead antibiotic candidate, ibezapolstat, preparing to advance to international Phase 3 clinical trials to treat patients with *C. difficile* Infection (CDI). The Company today announced the results of a study in a humanized mouse model and its publication in the Journal of Antimicrobial Agents and Chemotherapeutics entitled: *"Microbiome impact of ibezapolstat and other Clostridioides difficile infection-relevant antibiotics using humanized mice".* The primary author is Trenton Wolfe, a PhD student at the University of Montana. This study was funded by the National Institute of Allergy and Infectious Diseases (NIAID), the National Cancer Institute (NCI), National Center for Advancing Translational Sciences (NCATS), and the Company.

According to 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 ibezapolstat clinical trial program, and Acurx Scientific Advisory Board member: "This study provides critical evidence to begin to distinguish ibezapolstat from other C. difficile directed antibiotics, especially fidaxomicin. Although both ibezapolstat and fidaxomicin were narrower spectrum than vancomycin or metronidazole, ibezapolstat's effect on the microbiome was distinctly different than fidaxomicin. How this translates into

beneficial health effects or emergence of antimicrobial resistance will be an area of further study."

Acurx's Executive Chairman, Bob DeLuccia, stated: "These results of this first ever direct comparison of the gut microbiome effects of ibezapolstat in a validated humanized mouse model set the stage for potential competitive advantage of IBZ over all commonly used anti-CDI antibiotics, including fidaxomicin". He added: "These data also serve as a foundation upon which to build future planned preclinical and clinical studies at the appropriate time to further clarify ibezapolstat's favorable effect on the microbiome known to confer health benefits to patients with CDI."

This study was a head-to-head comparison of intestinal microbiome effects of IBZ with other CDI antibiotics and has not been done previously in non-clinical, in vivo models. The purpose of this study was to compare gut microbiome changes associated with IBZ to other anti-CDI antibiotics in groups of germ-free mice. Changes in alpha and beta microbiome diversities following IBZ treatment were less pronounced compared to those observed in VAN- or MET-treated groups. By the end of therapy, IBZ increased the relative abundance of *Bacteroidota* and *Actinomycetota* phyla. In microbiome-humanized mice, IBZ and FDX had smaller effects on gut microbiome diversity, a positive outcome, compared to VAN and MET. This analysis places IBZ in a similar category of microbiome disruption as FDX with notable favorable differences of IBZ over FDX and indicating a narrower spectrum of microbiome alteration compared to broader-spectrum agents like VAN and MET. However, notable differences were observed between the microbiome of IBZ- and FDX-treated groups, which may allow for differentiation of these two antibiotics in future studies, such as increased proportion of Actinomycetota bacteria which include *Bifidobacteria* and other species known to confer human health benefits.

THE PUBLICATION IS ON OUR WEBSITE: www.acurxpharma.com

About the AAC Journal:
Antimicrobial Agents and Chemotherapy (AAC) is an interdisciplinary journal devoted to the dissemination of knowledge relating to all aspects of antimicrobial and antiparasitic agents and chemotherapy. Generally, any report involving studies on or with antimicrobial, antiviral (including antiretroviral), or antiparasitic agents is within the purview of AAC. Studies involving animal models, pharmacological characterization, and clinical trials are appropriate for consideration.

Acurx previously announced that it had received positive regulatory guidance from the EMA during its Scientific Advice Procedure which confirmed that the clinical, non-clinical and CMC (Chemistry Manufacturing and Controls) information package submitted to EMA supports advancement of the ibezapolstat Phase 3 program and if the Phase 3 program is successful, supports the submission of a Marketing Authorization Application (MAA) for regulatory approval in Europe. The information package submitted to EMA by the Company to which agreement has been reached with EMA included details on Acurx's two planned international Phase 3 clinical trials, 1:1 randomized (designed as non-inferiority vs vancomycin), primary and secondary endpoints, sample size, statistical analysis plan and the overall registration safety database. With mutually consistent feedback from both EMA and FDA, Acurx is well positioned to commence our international Phase 3 registration program.

The primary efficacy analysis will be performed using a Modified Intent-To-Treat (mITT)

population. This will result in an estimated 450 subjects in the mITT population, randomized in a 1:1 ratio to either ibezapolstat or standard- of-care vancomycin, enrolled into the initial Phase 3 trial. The trial design not only allows determination of ibezapolstat's ability to achieve Clinical Cure of CDI as measured 2 days after 10 days of oral treatment, but also includes assessment of ibezapolstat's potential effect on reduction of CDI recurrence in the target population. In the event non-inferiority of ibezapolstat to vancomycin is demonstrated, further analysis will be conducted to test for superiority.

About the Ibezapolstat Phase 2 Clinical Trial
The completed multicenter, open-label single-*arm segment (Phase 2a) study was followed by a double-blind, randomized, active-controlled, non-inferiority, segment (Phase 2b)* at 28 US clinical trial sites which together comprise the Phase 2 clinical trial. (Link

to Clinicaltrials.gov/NCT042447542) This Phase 2 clinical trial was designed to evaluate the clinical efficacy of ibezapolstat in the treatment of CDI including pharmacokinetics and microbiome changes from baseline. from study centers in the United States. In the Phase 2a trial segment,10 patients with diarrhea caused by *C. difficile* were treated with ibezapolstat 450 mg orally, twice daily for 10 days. All patients were followed for recurrence for 28± 2 days. Per protocol, after 10 patients of the projected 20 Phase 2a patients completed treatment (100% cured infection at End of Treatment).

In the Phase 2b trial segment, which was discontinued due to success, 32 patients with CDI were enrolled and randomized in a 1:1 ratio to either ibezapolstat 450 mg every 12 hours or vancomycin 125 mg orally every 6 hours, in each case, for 10 days and followed for 28 ± 2 days following the end of treatment for recurrence of CDI. The two treatments were identical in appearance, dosing times, and number of capsules administered to maintain the blind.

The Company previously reported that the overall observed Clinical Cure rate in the combined Phase 2 trials in patients with CDI was 96% (25 out of 26 patients), based on 10 out of 10 patients (100%) in Phase 2a in the Modified Intent to Treat Population, plus 15 out of 16 (94%) patients in Phase 2b in the Per Protocol Population, who experienced Clinical Cure during treatment with ibezapolstat.

100% (25 of 25) ibezapolstat-treated patients in Phase 2 (Phase 2a and 2b) who had Clinical Cure at EOT) (End of Treatment) remained cured through one month after EOT, as compared to 86% (12 of 14) for the vancomycin patient group. Ibezapolstat was well-tolerated, with three patients each experiencing one mild adverse event assessed by the blinded investigator to be drug- related. All three events were gastrointestinal in nature and resolved without treatment. There were no drug-related treatment withdrawals or no drug-related serious adverse events, or other safety findings
of concern. In the Phase 2b vancomycin control arm, 14 out of 14 patients experienced Clinical Cure. The Company is confident that based on the
pooled Phase 2 ibezapolstat Clinical Cure rate of 96% and the historical vancomycin cure rate of approximately 81% (Vancocin® Prescribing Information, January 2021), we will demonstrate non-inferiority of ibezapolstat to vancomycin in Phase 3 trials in accordance with the applicable FDA Guidance for Industry (October 2022).

In the Phase 2 clinical trial (both trial segments), the Company also evaluated pharmacokinetics (PK) and microbiome changes and test for anti-recurrence microbiome properties, including the change from baseline in alpha diversity and bacterial abundance,

especially overgrowth of healthy gut microbiota Actinobacteria and Firmicute phylum species during and after therapy. Phase 2a data demonstrated complete eradication of colonic *C. difficile* by day three of treatment with ibezapolstat as well as the observed overgrowth of healthy gut microbiota, Actinobacteria and Firmicute phyla species, during and after therapy. Very importantly, emerging data show an increased concentration of secondary bile acids during and following ibezapolstat therapy which is known to correlate with colonization resistance against *C. difficile.* A decrease in primary bile acids and the favorable increase in the ratio of secondary-to-primary bile acids suggest that ibezapolstat may reduce the likelihood of CDI recurrence when compared to vancomycin. The company also recently reported positive extended clinical cure (ECC) data for ibezapolstat (IBZ), its lead antibiotic candidate, from the Company's recently completed Phase 2b clinical trial in patients with CDI. This exploratory endpoint showed that 12 patients who agreed to be followed up to three months following Clinical Cure of their infection, 5 of 5 IBZ patients experienced no recurrence of infection. In the vancomycin control arm of the trial, 7 of 7 patients experienced no recurrence of infection. ECC success is defined as a clinical cure at the TOC visit (i.e., at least 48 hours post EOT) and no recurrence of CDI within the 56 ± 2 days post EOT (ECC56) and 84 ± 2 days post EOT (ECC84) in patients who consented to extended observation. In the Phase 2b trial, 100% (5 of 5) of ibezapolstat-treated patients who agreed to observation for up to three months following Clinical Cure of CDI experienced no recurrence of infection. Furthermore, ibezapolstat-treated patients showed lower concentrations of fecal primary bile acids, and higher beneficial ratio of secondary to primary bile acids than vancomycin-treated patients.

About Ibezapolstat
Ibezapolstat is the Company's lead antibiotic candidate planning to advance to international Phase 3 clinical trials to treat patients with *C. difficil*e Infection (CDI). Ibezapolstat is a novel, orally administered antibiotic, being developed as a Gram-Positive Selective Spectrum (GPSS®) antibacterial. It is the first of a new class of DNA polymerase IIIC inhibitors under development by Acurx to treat bacterial infections. Ibezapolstat's unique spectrum of activity, which includes *C. difficile* but spares other Firmicutes and the importantActinobacteria phyla, appears to contribute to the maintenance of a healthy gut microbiome.

In June 2018, ibezapolstat was designated by the U.S. Food and Drug Administration (FDA) as a Qualified Infectious Disease Product (QIDP) for the treatment of patients with CDI and will be eligible to benefit from the incentives for the development of

new antibiotics established under the Generating New Antibiotic Incentives Now (GAIN) Act. Ir 2019, FDA granted "Fast Track" designation to ibezapolstat for the treatment of patients with CDI. The CDC has designated *C. difficile* as an urgent threat highlighting the need for new antibiotics to treat CDI.

About *Clostridioides difficile* Infection (CDI)
According to the 2017 Update (published February 2018) of the Clinical Practice Guidelines for C. difficile Infection by the Infectious Diseases Society of America (IDSA) and Society or Healthcare Epidemiology of America (SHEA), CDI remains a significant medical problem in hospitals, in long-term care facilities and in the community. *C. difficile* is one of the most common causes of health care- associated infections in U.S. hospitals (Lessa, et al, 2015,

New England Journal of Medicine). Recent estimates suggest *C. difficile* approaches

500,000 infections annually in the U.S. and is associated with approximately 20,000 deaths annually. (Guh, 2020, New England Journal of Medicine). Based on internal estimates, the recurrence rate for the antibiotics currently used to treat CDI is between 20% and 40% among approximately 150,000 patients treated. We believe the annual incidence of CDI in the U.S. approaches 600,000 infections and a mortality rate of approximately 9.3%.

About the Microbiome in *C. difficile* Infection (CDI) and Bile Acid Metabolism
C. difficile can be a normal component of the healthy gut microbiome, but when the microbiome is thrown out of balance, the *C. difficile* can thrive and cause an infection. After colonization with *C. difficile*, the organism produces and releases the main virulence factors, the two large clostridial toxins A (TcdA) and B (TcdB). (Kachrimanidou, Microorganisms 2020, 8, 200; doi:10.3390/microorganisms8020200.) TcdA and TcdB are exotoxins that bind to human intestinal epithelial cells and are responsible for inflammation, fluid and mucous secretion, as well as damage to the intestinal mucosa. Bile acids perform many functional roles in the GI tract, with one of the most important being maintenance of a healthy microbiome by inhibiting *C. difficile* growth. Primary bile acids, which are secreted by the liver into the intestines, promote germination of *C. difficile* spores and thereby

increase the risk of recurrent CDI after successful treatment of an initial episode. On the other hand, secondary bile acids, which are produced by normal gut microbiota through metabolism of primary bile acids, do not induce *C. difficile* sporulation and therefore protect against recurrent disease. Since ibezapolstat treatment leads to minimal disruption of the gut microbiome, bacterial production of secondary bile acids continues which may contribute to an anti-recurrence effect. Beneficial effects of bile acids include a decrease in primary bile acids and an increase in secondary bile acids in patients with CDI, which was observed in the Company's Ph2a trial results and previously reported (CID, 2022). In the Ph2b trial, ibezapolstat-treated patients showed lower concentrations of fecal primary bile acids, and higher beneficial ratio of secondary to primary bile acids than vancomycin-treated patients.

About Acurx Pharmaceuticals, Inc.
Acurx Pharmaceuticals is a late-stage biopharmaceutical company focused on developing a new class of small molecule antibiotics for difficult-to-

treat bacterial infections. The Company's approach is to develop antibiotic candidates with a Gram-positive selective spectrum (GPSS®) that blocks the active site of the Gram-positive specific bacterial enzyme DNA polymerase IIIC (pol IIIC), inhibiting DNA replication and leading to Gram-positive bacterial cell death. Its R&D pipeline includes antibiotic product candidates that target Gram-positive bacteria, including *Clostridioides difficile*, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin resistant Enterococcus (VRE), drug-resistant Streptococcus pneumoniae (DRSP) and *B. anthracis* (anthrax; a Bioterrorism Category A Threat-Level pathogen). Acurx's lead product candidate, ibezapolstat, for the treatment of *C. difficile* Infection is Phase 3 ready with plans in progress to begin international clinical trials next year. The Company's preclinical pipeline includes development of an oral product candidate for treatment of ABSSSI (Acute Bacterial Skin and Skin Structure Infections), upon which a development program for treatment of inhaled anthrax is being planned in parallel.

To learn more about Acurx Pharmaceuticals and its product pipeline, please visit www.acurxpharma.com.

Forward-Looking Statements
Any statements in this press release about our future expectations, plans and prospects, including statements regarding our strategy, future operations, prospects, plans and objectives, and other statements containing the words "believes," "anticipates," "plans," "expects," and similar expressions, constitute forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors, including: whether ibezapolstat will benefit from the QIDP designation; whether ibezapolstat will advance through the clinical trial process on a timely basis; whether the results of the clinical trials of ibezapolstat will warrant the submission of applications for marketing approval, and if so, whether ibezapolstat will receive approval from the FDA or equivalent foreign regulatory agencies where approval is sought; whether, if ibezapolstat obtains approval, it will be successfully distributed and marketed; and other risks and uncertainties described in the Company's annual report filed with the Securities and Exchange Commission on Form 10-K for the year ended December 31, 2023, and in the Company's subsequent filings with the Securities and Exchange Commission. Such forward-looking statements speak only as of the date of this press release, and Acurx disclaims any intent or obligation to update these forward-looking statements to reflect events or circumstances after the date of such statements, except as may be required by law.

Investor Contact:
Acurx Pharmaceuticals, Inc.
David P. Luci, President & CEO
Tel: 917-533-1469

Email: davidluci@acurxpharma.com

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