September 24, 2024 Acurx Pharmaceuticals

Acurx Announces Results of Its Pioneering Research with Ibezapolstat in Collaboration with Leiden University Medical Center at the Premier International C. difficile Symposium

- *Results feature high-resolution elucidation of interaction of ibezapolstat with its molecular target*
- *Mechanistic findings explain ibezapolstat's properties of lacking cross resistance with other antibiotics and not fostering the emergence of Enterococcus, including vancomycin-resistant strains, a unique differentiation among anti-CDI antibiotics*
- *Molecular structure data will be used to guide rational design of new systemic therapeutic compounds with improved inhibitory activity and PK characteristics*
- *Planning continues to prepare to advance ibezapolstat into international Phase 3 clinical trials for treatment of C. difficile Infection (CDI)*
- *Acurx is also preparing requests for regulatory guidance to initiate clinical trials in the European Union, the United Kingdom, Japan and Canada*
- *Ibezapolstat has previously received FDA QIDP and Fast-Track Designation from FDA*

STATEN ISLAND, N.Y., Sept. 24, 2024 /PRNewswire/ -- Acurx Pharmaceuticals, Inc. (NASDAQ: ACXP) ("Acurx" or the "Company"), a late-stage biopharmaceutical company developing a new class of small molecule antibiotics for difficult-to-treat bacterial infections, today announced results from its pioneering research with ibezapolstat in collaboration with Leiden University Medical Center (LUMC). These results were presented at the premier International *C. difficile* Symposium (ICDS) held in Bled, Slovenia on September 17-19, 2024. Dr. Wiep Klaas Smits, PhD, Associate Professor, LUMC, delivered a presentation entitled: Structure of the Replicative Polymerase PolC Reveals Mode of Action and Mechanism of Resistance of the Anti-CDI Agent Ibezapolstat and Related Inhibitors.

According to Dr. Smits: "Our findings with ibezapolstat regarding the structural biology of DNA pol IIIC inhibitors have important implications for the development of a new family of antibiotics to treat high priority, multi-drug resistant, gram-positive infections". He further stated: "I believe that DNA replication is a promising but underexplored target, and this novel class of DNA pol IIIC inhibitors could be an important new tool to address the pandemic of antimicrobial resistance"

Robert J. DeLuccia, Executive Chairman of Acurx, stated: "We are very pleased with the outcome of our collaboration with LUMC which has been exceptionally productive." He added: "This detailed demonstration of the mode of action of DNA pol IIIC inhibitors in general, and for ibezapolstat specifically, is critically important to support our scientific foundation and our regulatory filings as we advance into this late-stage of ibezapolstat's development pathway toward commercialization".

The presentation is available on the Acurx Pharmaceuticals website www.acurxpharma.com.

Acurx has previously announced that it had a successful FDA End-of-Phase 2 Meeting and Phase 3 Readiness for ibezapolstat for the Treatment of C. difficile Infection. Agreement with FDA was reached on key elements to move forward with its international Phase 3 clinical trial program. Agreement was also reached with FDA on the complete non-clinical and clinical development plan for filing of a New Drug Application (NDA) for marketing approval. Planning continues to advance ibezapolstat into international Phase 3 clinical trials for treatment of C. difficile Infection (CDI). Acurx is also now preparing to submit requests for regulatory guidance to initiate clinical trials in the European Union, the United Kingdom, Japan and Canada.

Key elements for the two Phase 3, non-inferiority, pivotal trials were confirmed and included agreement with FDA on the protocol design, patient population, primary and secondary endpoints, and size of the registration safety database. Based on FDA recommendations, and in anticipation of an EMA Scientific Advice Meeting, the primary efficacy analysis will be performed using a Modified Intent-To-Treat (mITT) population consistent with EMA requirements. 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 Research Project, Leiden University Medical Center, the Research Consortium

Health Holland awarded a grant of approximately $500,000 USD to Leiden University Medical Center which was co-funded by a PPP (Public Private Partnership) allowance made available by Health~Holland, Top Sector Life Sciences & Health, to stimulate public-private partnerships and to further study the mechanism of action of DNA pol IIIC inhibitors in scientific collaboration with Acurx Pharmaceuticals. https://www.health-holland.com/

This innovative research included study of 3-dimensional structures of DNA polymerases and their binding interactions with Acurx inhibitors. The antibacterial action of Acurx's pipeline of novel DNA pol IIIC inhibitors has been clinically validated by ibezapolstat's completion of a Ph2 clinical trial for treatment of C. difficile Infection (CDI). https://www.lumc.nl/en/research/.

The research outcome is intended to accelerate lead product candidate selection for Acurx's pre-clinical program for other WHO, CDC and FDA high-priority, multi-drug resistant Gram-positive pathogens where new classes of antibiotics are needed.

Together with Acurx Pharmaceuticals the PPP initiated the research project entitled "Bad bugs, new drugs: elucidation of the structure of DNA polymerase C of multidrug resistant bacteria in complex with novel classes of antimicrobials."

About the C. difficile Symposium (ICDS)

The International C. difficile Symposium (ICDS) is now established as the premier venue for the review of Clostridium difficile research.

The 1st meeting was held in Kranjska Gora in 2004, the 2nd in Maribor in 2007, while all earlier meetings were in Bled in 2010, 2012, 2015 and in 2018. ICDS in 2020 was held virtually. The 2024 meeting will provide the ideal opportunity to review progress in epidemiology, diagnostics, clinical trials, basic research and in understanding *C. difficile* pathogenesis and controlling the devastating disease it causes.

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. (see https://clinicaltrials.gov/ct2/show/NCT04247542). 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. and continue to test for anti-recurrence microbiome properties seen in the Phase 2a trial, including the treatment-related changes in alpha diversity and bacterial abundance and effects on bile acid metabolism.

The completed Phase 2a segment of this trial was an open label cohort of up to 20 subjects from study centers in the United States. In this cohort, 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). The Trial Oversight Committee assessed the safety and tolerability and made its recommendation regarding early termination of the Phase 2a study and advancement to the Ph2b segment. The Company's Scientific Advisory Board concurred with this recommendation.

In the now completed 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. 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).

The Phase 2b clinical trial segment was discontinued due to success. The Company made this decision in consultation with its medical and scientific advisors and statisticians based on observed aggregate blinded data and other factors, including the cost to maintain clinical trial sites and slow enrollment due to COVID-19 and its aftermath. The Company had determined that the trial performed as anticipated for both treatments, ibezapolstat and the control antibiotic vancomycin (a standard of care to treat patients with CDI), with high rates of clinical cure observed across the trial.

The Phase 2b trial was originally designed to be a non-inferiority (NI) trial and later amended to include an interim efficacy analysis with review by an Independent Data Monitoring Committee (IDMC). The decision to end the trial early based on blinded clinical observations obviated the need for an interim analysis, IDMC review, and NI assessment. The Company determined, in consultation with its clinical and statistical experts, that presenting clinical cure rates for the primary efficacy endpoint is the most appropriate representation for the clinical activity of ibezapolstat in treating CDI.

In the Phase 2 clinical trial, 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.

About Ibezapolstat

Ibezapolstat is the Company's lead antibiotic candidate planning to advance to international Phase 3 clinical trials to treat patients with C. difficile 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 important Actinobacteria

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. In January 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).

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) and drug-resistant Streptococcus pneumoniae (DRSP).

To learn more about Acurx Pharmaceuticals and its product pipeline, please visit https://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.

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