Venatorx Pharmaceuticals Announces FDA Acceptance and Priority Review of New Drug Application for Cefepime-Taniborbactam to Treat Complicated Urinary Tract Infections (cUTI), including Pyelonephritis, in Adults

Cefepime-taniborbactam has also demonstrated in vitro activity against CDC Urgent and Serious Threat Pathogens carbapenem-resistant Enterobacterales, multidrug-resistant Pseudomonas aeruginosa *and Extended Spectrum Beta-lactamase-producing Enterobacterales*

In the CERTAIN-1 cUTI Phase 3 study, cefepime-taniborbactam demonstrated clinical efficacy in patients with infections due to Extended Spectrum Beta-lactamase producing Enterobacterales and carbapenem-resistant Enterobacterales

PDUFA action date set for February 22, 2024

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MALVERN, Pa.--(BUSINESS WIRE)--Venatorx Pharmaceuticals, a private, pre-commercial pharmaceutical company focused on improving health outcomes for patients with difficult-to-treat drug resistant gram-negative bacterial infections and viral infections, today announced that the U.S. Food and Drug Administration (FDA) has accepted the company's New Drug Application (NDA) for cefepime-taniborbactam, an investigational beta-lactam/beta-lactamase inhibitor (BL/BLI) antibiotic for the potential treatment of adult patients with complicated urinary tract infections (cUTI), including pyelonephritis. The FDA previously granted Qualified Infectious Disease Product and Fast Track designations to cefepime-taniborbactam. The FDA has granted Priority Review of the NDA with a Prescription Drug User Fee Act (PDUFA) target action date of February 22, 2024.

"The NDA acceptance represents the culmination of unwavering dedication, scientific excellence, and the collaborative efforts of our talented team, partners, and clinical investigators," said Christopher J. Burns, Ph.D., Chief Executive Officer of Venatorx. "Cefepime-taniborbactam exemplifies our commitment to innovation and improving patient outcomes. By addressing the evolving and increasing challenges posed by antimicrobial resistance, we aim to make a meaningful impact on global public health."

The cefepime-taniborbactam NDA is supported by results from the pivotal Phase 3 study, CERTAIN-1, evaluating the efficacy and safety of cefepime-taniborbactam compared to meropenem in adults with cUTI, including acute pyelonephritis. Cefepime-taniborbactam was superior to meropenem for the primary efficacy endpoint of composite microbiologic and clinical success at the Test of Cure (TOC) visit (Day 19-23) in the microbiological intent-to-treat (microITT) population. Cefepime-taniborbactam was well-tolerated and no new safety findings were identified.

“Due to its broad spectrum of *in-vitro* activity against established and rapidly increasing mechanisms of carbapenem resistance such as serine- and metallo-beta-lactamases and the positive results demonstrated in CERTAIN-1, cefepime-taniborbactam, if approved, will address a critical unmet need and be a potentially essential treatment option in the continuing fight against antimicrobial resistance in gram-negative bacterial infections,” said Paul McGovern, M.D., Senior Vice President, Medical Sciences at Venatorx. “Patients with cUTIs, including pyelonephritis, and their healthcare providers should have a new treatment option when confronted with infections due to these antibacterial resistant infections.”

About the CERTAIN-1 Phase 3 Clinical Trial

CERTAIN-1 (Cefepime Rescue with Taniborbactam in cUTI) was a global, randomized, double-blind, active-controlled non-inferiority Phase 3 study evaluating the efficacy, safety, and tolerability of cefepime-taniborbactam compared to meropenem in adults with cUTI, including acute pyelonephritis. The trial enrolled 661 adult patients who were randomized 2:1 to receive cefepime-taniborbactam 2.5g q8h or meropenem 1g q8h for 7 days (up to 14 days for patients with bacteremia). The primary efficacy endpoint evaluated the composite clinical and microbiologic response (i.e., bacterial eradication) at the Test of Cure (TOC) visit (Day 19-23) in the microbiological intent-to-treat (microITT) population.

Cefepime-taniborbactam met the primary efficacy endpoint of statistical noninferiority (NI) to meropenem in the microITT population at TOC with composite microbiologic and clinical success occurring in 70.6% of cefepime-taniborbactam treated patients and 58.0% of meropenem treated patients (treatment difference 12.6; 95% CI, 3.1, 22.2). A prespecified superiority assessment was conducted following confirmation of NI. Superiority was concluded as the lower bound of the 95% CI for noninferiority was greater than zero. The pre-specified superiority test (two-sided p-value = 0.0088) demonstrated the strength of evidence associated with the superiority conclusion for the composite endpoint at TOC. The efficacy of cefepime-taniborbactam was sustained for the composite microbiologic and clinical response at the Late-Follow-Up (Day 28-35) visit.

Rates of treatment-emergent adverse events (TEAEs) were 35.5% for cefepime-taniborbactam and 29.0% for meropenem. Serious TEAEs occurred in 2.0% and 1.8% of cefepime-taniborbactam and meropenem treated patients, respectively. Treatment discontinuations due to TEAEs occurred in 3.0% of cefepime-taniborbactam patients and 0.9% of meropenem treated patients. There was one death in the cefepime-taniborbactam treatment group, which was unrelated to study treatment as assessed by the investigator.

About Cefepime-Taniborbactam

Cefepime-taniborbactam is an investigational intravenous (IV) beta-lactam/beta-lactamase inhibitor (BL/BLI) antibiotic combination being developed for the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis, and hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP). Cefepime-taniborbactam was accepted for review by the US FDA for cUTI, including pyelonephritis with a PDUFA date of February 22, 2024.

Cefepime, a fourth-generation cephalosporin, is a widely used beta-lactam (BL) antibiotic with more than two decades of proven safety and clinical utility against susceptible gram-negative and gram-positive bacteria. Taniborbactam is a beta-lactamase inhibitor (BLI) that, in combination with cefepime, is being studied as a potential treatment option for patients with serious bacterial infections caused by antibiotic resistant gram-negative bacteria, most notably extended spectrum

beta-lactamase (ESBL)-expressing Enterobacterales, carbapenem-resistant Enterobacterales (CRE), and multidrug-resistant (MDR) *Pseudomonas aeruginosa* (MDR-PA), which can include carbapenem-resistant *P. aeruginosa* (CRPA).

About Gram-Negative Infections and Antimicrobial Resistance (AMR)

In a recent report on AMR, the U.S. Centers for Disease Control and Prevention (CDC) reported rates of resistance have increased significantly in the U.S. among bacterial pathogens including those commonly causing cUTI, pyelonephritis, and bacteremia. The CDC also cited that there are more than 2.8 million AMR infections annually in the U.S., which are directly related to more than 35,000 deaths.[1] Between 2014 and 2019, an analysis of U.S. UTI patients determined that 4.4% of cases were carbapenem resistant (CR) and 24.5% of U.S. UTI patients were bacteremic with 1.7% of cases caused by a CR pathogen. Patients with CR infections had a significantly longer hospital length of stay (LOS), were less likely to be discharged home, had a higher readmission rate, and had greater LOS-associated charges than patients with carbapenem-susceptible infections. Additionally, patients with bacteremia (urosepsis) due to CR pathogens had a significantly higher rate of mortality than those with carbapenem susceptible pathogens.[2]

Gram-negative bacteria have multiple AMR mechanisms that continue to adapt in response to increases in antibiotic usage. Carbapenems are broad-spectrum antibiotics that have been widely used to treat infections caused by multidrug-resistant gram-negative bacteria, including Enterobacterales. With the increased global use of carbapenems, CRE have emerged, which have limited treatment options and are associated with increased morbidity and mortality. Resistance to carbapenems among Enterobacterales is primarily achieved by production of carbapenemases, which are enzymes capable of hydrolyzing carbapenem antibiotics and most other beta-lactams and fall into two distinct families: serine beta-lactamases and metallo-beta-lactamases (MBLs). Common variants of MBLs include New Delhi MBL (NDM) and Verona Integron-encoded MBL (VIM). According to an IHMA surveillance study in 2018-2019 and JMI US Surveillance study from 2021, MBLs were the most commonly identified carbapenem resistance mechanism globally among Enterobacterales isolates, with ~16 to 18% of US CRE isolates carrying MBLs. [3,4]

While CRPA is also increasing in some geographies due to emergence of MBLs, MDR-PA, which may exhibit resistance to carbapenems, represents an increasing challenge for clinicians and their patients in the US and globally due to the paucity of treatment options for this primarily hospital-associated pathogen. Especially outside the US, CRPA may carry carbapenemases including MBLs (i.e., VIM); however, non-carbapenemase resistance mechanisms (i.e., efflux pumps, porins) also contribute to the growing global resistance of MDR-PA and CRPA.[5]

If AMR infections continue on this trajectory, it has been projected that an estimated 10 million people will die per year of resistant infections by 2050—a number that surpasses the projected annual number of deaths (8.2 million) caused by cancer—and the cumulative cost to the global economy could be as high as US$100 trillion.[6] In the U.S., estimates have reached as high as US$20 billion in excess direct healthcare costs, with an additional US$35 billion associated with lost productivity.[7] By 2050, the world is at risk of losing up to 3.8% of its annual gross domestic product with an annual shortfall of up to US$3.4 trillion by 2030, a figure on par with losses attributable to the 2008 global financial crisis.[8]

The Infectious Disease Society of America (IDSA) maintains updated guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections online at https://www.idsociety.org/practice-

guideline/amr-guidance/.[9] For those patients who do not respond to current treatment, new antibiotic therapies are needed to combat AMR.

About Complicated Urinary Tract Infections

Complicated UTIs, which include pyelonephritis, are defined as urinary tract infections ascending from the bladder accompanied by local and systemic signs and symptoms, including fever, chills, malaise, flank pain, back pain, and/or costovertebral angle pain or tenderness, that usually occur in the presence of a functional or anatomical abnormality of the urinary tract or in the presence of catheterization. Bacteremia can arise secondary to infections like cUTI and can result in substantial morbidity and mortality.[2] Annually in U.S., it is estimated that more than 3 million cUTI patients will be diagnosed and require antibiotic therapy leading to over $6 billion in annualized 30-day costs.[10]

Funding Partners and Collaborators for Cefepime-Taniborbactam

Development of cefepime-taniborbactam began with federal funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services under contract number HHSN272201300019C, and Wellcome Trust under award number 360G-Wellcome-101999/Z/13/Z, and continues with federal funds from the Biomedical Advanced Research and Development Authority, Administration for Strategic Preparedness and Response, Department of Health and Human Services under contract number HHSO100201900007C.

In September 2018, Venatorx entered into an exclusive license agreement with Everest Medicines to support the development, registration, and commercialization of cefepime-taniborbactam in People's Republic of China, Macau, Hong Kong, Taiwan, South Korea, and select countries in Southeast Asia (the "Territory").

In April 2020, Venatorx and GARDP announced a collaboration to accelerate the development of, and access to, cefepime-taniborbactam for adult and pediatric populations. Venatorx has granted GARDP exclusive rights to distribute and sub-distribute cefepime-taniborbactam, once it is approved for clinical use, in low- and lower middle-income countries

About Venatorx Pharmaceuticals, Inc.

Venatorx is a private, pre-commercial pharmaceutical company focused on improving health outcomes for patients with difficult-to-treat drug resistant gram-negative bacterial infections and viral infections. Venatorx's lead asset, cefepime-taniborbactam, is an investigational antibiotic that completed a Phase 3 study (NCT03840148) in adults with complicated urinary tract infections (cUTI), including pyelonephritis and is under FDA review with a PDUFA action date of February 22, 2024. In October 2022, BARDA awarded a contract of up to $318M to Venatorx for development and procurement of cefepime-taniborbactam for the treatment of melioidosis and multidrug-resistant infections. As part of its broader pipeline, Venatorx is also developing an oral antibacterial, ceftibuten-ledaborbactam etzadroxil, that is currently in Phase 1 clinical studies. For more information about Venatorx and its anti-infectives portfolio, please visit www.venatorx.com.

Forward Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this press release that do not relate to matters of historical fact should be considered forward-looking statements, including without limitation statements regarding the potential, safety, efficacy, and regulatory and clinical development of Venatorx Pharmaceuticals' product candidates.

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Contacts

Media
Jennifer Guinan
Sage Strategic Marketing
jennifer@sagestrat.com
610.425.8659