Spero Therapeutics Announces Positive Topline Results from its Phase 3 ADAPT-PO Clinical Trial of Oral Tebipenem HBr in Complicated Urinary Tract Infection and Acute Pyelonephritis

September 8, 2020

Pivotal Phase 3 clinical trial of oral tebipenem HBr met primary endpoint, demonstrating statistical non-inferiority versus intravenous ertapenem in patients with complicated urinary tract infection and acute pyelonephritis

Well-tolerated with comparable safety profile to intravenous ertapenem

Spero intends to complete NDA submission for U.S. regulatory approval of tebipenem HBr in the second quarter of 2021

Management to host conference call and live webcast at 8:00 a.m. EDT today

CAMBRIDGE, Mass., Sept. 08, 2020 (GLOBE NEWSWIRE) -- Spero Therapeutics, Inc. (Nasdaq: SPRO), a multi-asset clinical-stage biopharmaceutical company focused on identifying, developing and commercializing treatments in high unmet medical need areas involving multidrug-resistant (MDR) bacterial infections and rare diseases, today announced positive topline results from ADAPT-PO, the pivotal Phase 3 clinical trial evaluating Spero's oral antibiotic candidate, tebipenem HBr, for the treatment of adults with complicated urinary tract infection (cUTI) and acute pyelonephritis (AP). Topline data from the trial demonstrate that oral tebipenem HBr was statistically non-inferior to intravenous (IV) ertapenem in the treatment of patients with cUTI and patients with AP.

The global Phase 3 ADAPT-PO clinical trial evaluated the safety and efficacy of oral tebipenem HBr versus IV ertapenem for the treatment of adults with cUTI or AP. Results demonstrate that tebipenem HBr was non-inferior compared to ertapenem with respect to the trial's primary endpoint, overall response (combined clinical cure plus microbiologic eradication) at the test-of-cure (TOC) visit in the microbiological-intent-to-treat (micro-ITT) population.

- The favorable overall response rates at TOC were 58.8% (264/449) versus 61.6% (258/419) for tebipenem HBr and ertapenem, respectively (treatment difference, -3.3%; 95% confidence interval [CI]: -9.7, 3.2; -12.5% NI margin).
- Clinical cure rates at TOC were high (>93%) in both treatment groups.
- Overall response rates were consistent across key subgroups of interest, including age, baseline diagnosis, and presence of bacteremia. Per pathogen microbiological response was balanced across treatment groups for most prevalent uropathogens.

"The results of ADAPT-PO are truly exciting and welcome news for the medical community and for the millions of U.S. patients suffering from cUTI and AP annually," said Dr. Keith Kaye, Director of Research in the Division of Infectious Diseases at the University of Michigan Medical School. "Due to the increasing prevalence of antibiotic-resistant bacteria, many patients with cUTI now receive intravenous antibiotics as their only available treatment option. The much-anticipated data from this head-to-head comparison against an IV standard-of-care carbapenem antibiotic suggest that in many instances oral, outpatient treatment of these complicated bacterial infections is a viable option."

Comparative safety data from the 1,372 hospitalized adult patients who enrolled in the trial suggest that tebipenem HBr was well-tolerated, with a safety profile similar to that of ertapenem.

- Treatment emergent adverse events (TEAEs) were reported in approximately 26% of patients in both treatment groups.
- The most commonly reported TEAEs in both treatment groups were diarrhea (5.0%) and headache (3.8%).
- Serious TEAEs were infrequent (1.3% for tebipenem HBr vs. 1.7% for ertapenem) and no deaths were reported in the trial.
- Three *Clostridioides difficile*-associated TEAEs were observed in the ertapenem group, while none were observed in the tebipenem HBr group.

Dr. Ankit Mahadevia, Chief Executive Officer of Spero Therapeutics, commented, "The ADAPT-PO trial is a landmark trial that is the first ever to test an all oral regimen against an all IV regimen for the treatment of cUTI. We are thrilled to announce positive ADAPT-PO results that we believe demonstrate the value of tebipenem HBr for healthcare providers, payers and patients. These results bring us one step closer to delivering a new oral therapeutic option that could potentially address an expanding unmet need for patients with cUTI and AP. If approved by the FDA, tebipenem HBr would be the first oral cUTI drug to earn approval in 26 years, which would be an important achievement given the high levels of resistance to currently available oral therapies. We want to express our gratitude to the patients and investigators who participated in the trial."

Emerging data from the tebipenem HBr program, including the ADAPT-PO clinical trial results, will be presented in detail at future scientific meetings and in publications. Tebipenem HBr has been granted Qualified Infectious Disease Product (QIDP) and Fast Track designations by the U.S. Food and Drug Administration (FDA) for the treatment of cUTI, which may result in expedited review and an option for rolling submission of a New Drug Application (NDA). Spero intends to initiate a rolling NDA submission and anticipates completing the NDA submission to the FDA for tebipenem HBr in the second quarter of 2021.

Conference Call and Webcast
Spero will host a conference call and webcast today at 8:00 a.m. EDT. To access the call, please dial 1-877-705-6003 (domestic) or 1-201-493-6725 (international) and refer to conference ID 13709990. The conference call will also be webcast live and a link to the webcast can be accessed (here) and also on Spero's website at www.sperotherapeutics.com in the "Investors and Media" section under "Events and Presentations." An archived webcast will be available on Spero's website for 30 days following the presentation.

About ADAPT-PO
The global, randomized, placebo-controlled ADAPT-PO Phase 3 clinical trial evaluated the safety and efficacy of tebipenem HBr in hospitalized adult patients with cUTI or AP. Patients were randomized (1:1) to receive tebipenem HBr (600 mg) orally every 8 hours, or ertapenem (1 g) IV every 24 hours, for a total of 7 to 10 days. Patients with concurrent bacteremia received up to 14 days of therapy. The primary endpoint was the overall response, defined as the combination of clinical cure and microbiological eradication of the causative pathogen(s), at the test-of-cure (TOC) visit (Day 19 ±2 days) and was assessed in the micro-ITT population. The primary analysis and assessment of non-inferiority was evaluated using a pre-specified -12.5% non-inferiority (NI) margin. This NI margin was a modification of the original NI margin of -10% that was discussed with the FDA because of concern that the COVID-19 pandemic could have an adverse effect on the trial. As a result, the NI margin was modified prior to database lock from the original NI margin. However, as noted by the lower bound of the 95% confidence interval (-9.7), the trial also achieved success according to the original -10% NI margin.

About Tebipenem HBr
Tebipenem HBr (tebipenem pivoxil hydrobromide; formerly SPR994) is Spero's novel investigational oral formulation of tebipenem pivoxil, a carbapenem antibiotic of the β-lactam class marketed by Meiji Seika Pharma Co. Ltd. (Meiji) in Japan as Orapenem® since 2009 for pediatric infections limited to pneumonia, otitis media and sinusitis. Carbapenems are an important subclass of antibiotics because they have been observed to be safe and effective in the treatment of drug-resistant Gram-negative bacterial infections. Tebipenem HBr is being developed for the treatment of complicated urinary tract infections, including acute pyelonephritis. The Company expects that the favorable ADAPT-PO clinical trial results, once finalized, will support completion of a New Drug Application submission to the FDA in the second quarter of 2021. If approved, tebipenem HBr would be the first oral carbapenem antimicrobial to receive marketing approval in the United States. Tebipenem HBr has been granted Qualified Infectious Disease Product (QIDP) and Fast Track designations by the FDA for the treatment of cUTI and AP.

About Complicated Urinary Tract Infection (cUTI)
In 2007, in the United States alone, there were an estimated 10.5 million office visits for urinary tract infection (UTI) symptoms and 2-3 million emergency department visits. Most cases of cUTI and acute pyelonephritis are caused by *Enterobacteriaceae*, with *Escherichia coli* being the most common pathogen in the majority of infections across care settings. According to the Centers for Disease Control (CDC), drug-resistant *Enterobacteriaceae*, or commonly called extended-spectrum beta lactamase (ESBL) producing *Enterobacteriaceae*, is considered to be one of the most serious antibiotic-resistant bacterial threats in the United States. Antimicrobial resistance rates across most U.S. regions to fluoroquinolones, the most commonly used antibiotic for UTI, are >30% among *Escherichia coli*. Currently, there are few oral options to treat these patients. There is a need for strategies to avoid preventable cUTI-related inpatient and emergency department visits and potentially an opportunity to shift site of care for a proportion of hospitalized patients with cUTIs.

Tebipenem HBr Research Support
This project has been funded in part with Federal funds from the Department of Health and Human Services; Office of the Assistant Secretary for Preparedness and Response; Biomedical Advanced Research and Development Authority, under Contract No. HHSO100201800015C.

About Spero Therapeutics
Spero Therapeutics, Inc. is a multi-asset, clinical-stage biopharmaceutical company focused on identifying, developing and commercializing novel treatments for multidrug-resistant (MDR) bacterial infections and rare diseases.

Spero's lead product candidate, tebipenem HBr (tebipenem pivoxil hydrobromide; formerly SPR994), is anticipated to be the first oral carbapenem antibiotic for use in adults to treat serious bacterial infections, including those caused by MDR Gram-negative infections.

Spero is also advancing SPR720, its novel oral therapy product candidate designed for the treatment of rare, orphan pulmonary disease caused by non-tuberculous mycobacterial (NTM) infections.

Spero also has an IV-administered next generation polymyxin product candidate, SPR206, developed from its potentiator platform that is being developed to treat MDR Gram-negative infections in the hospital setting.

For more information, visit ***https://sperotherapeutics.com***.

Forward-Looking Statements
This press release may contain forward-looking statements. These statements include, but are not limited to, statements about the initiation, timing and submission to the FDA of a NDA for tebipenem HBr and the potential approval of tebipenem HBr by the FDA; future commercialization, the potential number of patients who could be treated by tebipenem HBr and market demand for tebipenem HBr generally; expected broad access across payer channels for tebipenem HBr; the expected pricing of tebipenem HBr and the anticipated shift from IV to oral administration. In some cases, forward-looking statements can be identified by terms such as "may," "will," "should," "expect," "plan," "aim," "anticipate," "could," "intent," "target," "project," "contemplate," "believe," "estimate," "predict," "potential" or "continue" or the negative of these terms or other similar expressions. Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors, including Spero's ability to timely complete related Phase 1 trials for NDA submission, taking into account the possible effects of the COVID-19 pandemic; Spero's need for additional funding; the lengthy, expensive, and uncertain process of clinical drug development; Spero's reliance on third parties to manufacture, develop, and commercialize its product candidates, if approved; the ability to develop and commercialize Spero's product candidates, if approved; the potential impact of the COVID-19 pandemic; Spero's ability to retain key personnel and to manage its growth; and other factors discussed in the "Risk Factors" set forth in filings that Spero periodically makes with the U.S. Securities and Exchange Commission. The forward-looking statements included in this press release represent Spero's views as of the date of this press release. Spero anticipates that subsequent events and developments will cause its views to change. However, while Spero may elect to update these forward-looking statements at some point in the future, it specifically disclaims any obligation to do so. These forward-looking statements should not be relied upon as representing Spero's views as of any date subsequent to the date of this press release.

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