TFF Pharmaceuticals Announces Promising Topline Results from Phase 1 Clinical Trial of Inhaled Tacrolimus Powder and Progression Toward Phase 2 in Lung Transplantation

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Inhaled Tacrolimus Shows Dose-Dependent PK that Achieves Desired Therapeutic Plasma Concentrations and Promising Safety Profile in both SAD and MAD Components of Phase 1

AUSTIN, Texas, Sept. 23, 2021 (GLOBE NEWSWIRE) -- TFF Pharmaceuticals, Inc. (NASDAQ: TFFP), a clinical-stage biopharmaceutical company focused on developing and commercializing innovative drug products based on its patented Thin Film Freezing (TFF) technology platform, today announced topline results from the recently completed Phase 1 clinical trial for Tacrolimus Inhalation Powder showing a promising safety profile and demonstrating therapeutic drug levels can be achieved at low doses.

Among the approximately 4,000 lung transplantation procedures performed each year worldwide, high tacrolimus blood concentrations are common and known to be associated with Acute Kidney Injury (AKI) that can progress to Chronic Kidney Disease (CKD)[1,2]. Inhaled Tacrolimus Powder, which is delivered directly to the lung, offers a potentially attractive option for lung transplantation patients by maintaining higher concentrations at the site of the graft while not exposing other organs to supra-therapeutic plasma levels that are well known to cause renal damage in a substantial portion of these patients.

Therapeutic drug monitoring (TDM) is a routine practice in lung transplant recipients where tacrolimus dosing is continually titrated to maintain plasma concentrations within a narrow therapeutic window. Tacrolimus trough plasma concentrations in a range of 5-15 ng/mL are generally regarded as necessary for effective immunosuppression and a range of 10-15 ng/mL is used in the first year following transplant to minimize rejection[3,4]. However, the challenge for lung transplant patients is to ensure sufficiently high local concentrations of tacrolimus are maintained in the lung to prevent acute allograft rejection without inducing renal toxicity.

“The data from this Phase 1 study suggests that Tacrolimus Inhalation Powder can be administered with an acceptable safety profile to achieve the appropriate balance of local and systemic concentrations for immunosuppression at the site of the lung transplant while minimizing the risk of supra-therapeutic systemic exposure well known to cause substantial renal toxicity in these patients,” said Glenn Mattes, Chief Executive Officer of TFF Pharmaceuticals. “We believe the strong dose-dependent PK data with pulmonary administration will allow a flexible dosing regimen that can be tailored to each patient, consistent with the manner in which these patients are managed in the real-world setting. This flexible dosing approach will also be reflected in the design for our upcoming Phase 2 study in lung transplant recipients.”

The trial was conducted with the standard format for a Phase 1 program:

- A single ascending dose (SAD) phase with single inhalation doses of Tacrolimus Inhalation Powder of 0.5 mg, 1 mg, 2.5 mg and 5 mg was administered to four cohorts of healthy volunteers. The eight subjects in each cohort included six subjects randomized to receive tacrolimus and two randomized to receive placebo. A total of 24 subjects received active study drug.
- A multiple ascending dose (MAD) phase with three total cohorts. Two cohorts received repeated administration of Tacrolimus Inhalation Powder every 12 hours over 7 days at doses of 0.5 mg and 1.0 mg (BID dosing), and a third cohort received repeated administration of 1.5 mg once daily for seven days (QD dosing). The eight subjects in each cohort included six subjects randomized to receive tacrolimus and two randomized to receive placebo. A total of 18 subjects received active study drug.

Topline pharmacokinetic data from the Phase 1 study included:

- In the SAD phase of the study, inhaled delivery of tacrolimus resulted in mean trough blood levels of 10 ng/mL 12 hours post-dosing for subjects that received a dose of 5 mg, which falls within the desired range for maintenance immunosuppression following lung transplant.
- As previously reported in July, subjects from the MAD phase of the study who received doses of 0.5 mg twice daily and 1.0 mg twice daily achieved 12-hour trough steady state blood levels of tacrolimus that averaged 6.8 and 14.9 ng/mL, respectively, demonstrating that Inhaled Tacrolimus Powder can achieve blood levels generally deemed to be sufficient for efficacious immunosuppression.
- New data reported today showed that once daily dosing with 1.5 mg of Inhaled Tacrolimus Powder resulted in mean 12-hour trough blood levels of 6.3 ng/mL and mean 24-hour trough blood levels of 4.8 ng/mL, consistent with the desired therapeutic ranges for lung transplant patients.

The company is confident that this collective range of dose options has the potential to provide the flexibility for effective management of lung

transplant patients in keeping with the current standard of practice that uses TDM to maintain appropriate plasma concentrations of tacrolimus.

TFF Pharmaceuticals expects to take critical steps toward beginning its Phase 2 clinical study of Inhaled Tacrolimus Powder by the end of 2021. The goal of the Phase 2 study, which will be an open-label study conducted in lung transplant patients who are experiencing kidney toxicity, is to test the hypothesis that Inhaled Tacrolimus Powder can provide adequate systemic exposure while maintaining higher drug levels in the lung, thereby reducing the risk of acute allograft rejection and improving symptoms of renal toxicity. Patients currently receiving oral tacrolimus will transition to a flexible dosing regimen of inhaled tacrolimus. The inhalation dose will be able to be adjusted weekly to achieve the desired blood level assigned by each patient's physician and ongoing biomarker-based assessments.

"It is exciting for our patients and for us as clinicians to have a potential new option with Inhaled Tacrolimus Powder. Inhaled tacrolimus may be able to help overcome multiple current limitations we encounter with therapy and could optimize the management of acute allograft rejection in lung transplant recipients," said Deborah Jo Levine, M.D., Professor of Medicine in the Division of Pulmonary and Critical Care Medicine and Medical Director of Lung Transplantation and Director of the Pulmonary Hypertension Center with the UT Health San Antonio Long School of Medicine. "In addition to concerns about systemic toxicities including kidney injury, oral administration of tacrolimus is often challenging for patients to manage with multiple adjustments. We currently have a lack of innovative therapies in this space and these studies reveal some of the most exciting results we have seen in the lung transplantation field. I look forward to seeing how inhaled tacrolimus performs in the next stage of development when utilized in lung transplant recipients."

Safety results from the Phase 1 trial included:

- In both phases of the trial, the reported adverse events (AEs) were generally mild and consistent with those known to be related to tacrolimus exposure. There was no evidence of decreased pulmonary function, and based on the ECG assessments administered to all subjects, there were no instances of QTc prolongation (a known effect of tacrolimus).
- In the SAD portion of the study, no serious adverse events (SAEs) occurred. The most common side effects were mild and included headache, altered taste, throat irritation, and chest tightness.
- In the MAD portion of the trial, four patients experienced mild hypomagnesemia, a known adverse effect of tacrolimus. All four patients were in the 1.0 mg BID dosing cohort. Importantly, three of the four subjects had 12-hour trough blood levels of tacrolimus that exceeded the upper limit of the optimal range for lung transplant patients (15 ng/mL). All four patients, after receiving magnesium supplementation, had their magnesium levels return to baseline.
- Other mild AEs in the MAD portion of the study included headache, altered taste, throat irritation, and chest tightness. One subject experienced a headache with moderate severity that was deemed unrelated to study medication.
- A single Serious Adverse Event (SAE) was reported as possibly drug-related in a subject in the 1.5 mg QD dose cohort of the MAD phase of the study. The subject experienced confusion approximately 3.5 hours after receiving the seventh dose. The effects resolved spontaneously within 30 minutes and the subject was not admitted to hospital. During this event, no abnormal lab results, ECG traces, or physical exam results were found. This, combined with the transient nature and spontaneous resolution without changes in drug concentrations, leads to an unclear relationship between the drug and the adverse event. A review by the safety management committee concluded that it was safe to continue dosing the remainder of the cohort.

1. Eur J Clin Pharmacol. 2017; 73(5): 573–580.
2. International Society for Heart & Lung Transplantation (ISHLT.org)
3. Ann. Thorac. Med.; Jul-Sep 2019;14(3):186-191
4. University of Pittsburgh Medical Center; Lung Transplant Management Guidelines; August 2016

About TFF Pharmaceuticals' Thin Film Freezing Technology Platform
TFF Pharmaceuticals' Thin Film Freezing (TFF) platform was designed to improve the solubility and absorption of poorly water-soluble drugs and is particularly suited to generate dry powder particles with properties targeted for inhalation delivery, especially to the deep lung, an area of extreme interest in respiratory medicine. The TFF process results in a "Brittle Matrix Particle," which possesses low bulk density, high surface area, and typically an amorphous morphology, allowing the particles to supersaturate when contacting the target site, such as lung tissue. Based upon laboratory experiments the aerodynamic properties of the particles are such that the portion of a drug deposited to the deep lung has the potential to reach as high as 75 percent.

About TFF Pharmaceuticals
TFF Pharmaceuticals, Inc. is a clinical-stage biopharmaceutical company focused on developing and commercializing innovative drug products based on its patented Thin Film Freezing, or TFF, technology platform. Early testing confirms that the TFF platform can significantly improve the solubility and absorption of poorly water-soluble drugs, a class of drugs that comprises approximately one-third of the major pharmaceuticals worldwide, thereby improving their pharmacokinetics. TFF Pharmaceuticals has two lead drug candidates: Voriconazole Inhalation Powder and Tacrolimus Inhalation Powder. The Company plans to add to this pipeline by collaborating with large pharmaceutical partners. The TFF Platform is protected by 42 patents issued or pending in the US and internationally. To learn more about TFF Pharmaceuticals and its product candidates, visit the Company's website at https://tffpharma.com.

SAFE HARBOR
This press release contains forward-looking statements regarding TFF Pharmaceuticals, Inc., including the benefits of the Company's TFF platform and its dry powder versions of Tacrolimus, and the Company's plans to add to its existing pipeline of product candidates. Those forward-looking statements involve known and unknown risks, uncertainties and other factors that could cause actual results to differ materially. Among those factors are: (i) the risk that the Company may not be able to successfully conclude clinical testing or obtain pre-market approval of its dry powder versions of

Tacrolimus, (ii) no drug product incorporating the TFF platform has received FDA pre-market approval or otherwise been incorporated into a commercial drug product, (iii) the Company has no current agreements or understandings with any large pharmaceutical companies for the development of a drug product incorporating the TFF Platform, (iv) the risk that the Company will not be able to conclude a long-term commercial agreement with any third-party, and (v) those other risks disclosed in the section “Risk Factors” included in the Company’s 2020 Annual Report on Form 10-K filed with the SEC on March 10, 2021. TFF Pharmaceuticals cautions readers not to place undue reliance on any forward-looking statements. TFF Pharmaceuticals does not undertake, and specifically disclaims, any obligation to update or revise such statements to reflect new circumstances or unanticipated events as they occur, except as required by law.

Company Contacts:

Glenn Mattes
President and CEO
TFF Pharmaceuticals, Inc.
gmattes@tffpharma.com
737-802-1973

Kirk Coleman
Chief Financial Officer
TFF Pharmaceuticals, Inc.
kcoleman@tffpharma.com
817-989-6358

Investor Relations Contact:
Corey Davis, Ph.D.
LifeSci Advisors
212-915-2577
cdavis@lifesciadvisors.com

Media Contact:
Gwendolyn Schanker
LifeSci Communications
(269) 921-3607
gschanker@lifescicomms.com

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