# Travere Therapeutics Announces Confirmatory Data from the Phase 3 PROTECT Study of FILSPARI® Demonstrating Long-Term Kidney Function Preservation in IgA Nephropathy; Narrowly Missing eGFR Total Slope Endpoint versus Active Control, Irbesartan

September 21, 2023

- *FILSPARI® (sparsentan) achieved a clinically meaningful difference vs. irbesartan in eGFR total slope (1.0 mL/min /1.73m$^2$ per year) [p= 0.058] and eGFR chronic slope (1.1 mL/min/1.73m$^2$ per year) [p=0.037]. Patients treated with FILSPARI over two years exhibited one of the slowest annual rates of kidney function decline seen in a clinical trial of IgAN patients (-2.7 to -2.9 mL/min/1.73m$^2$ per year)*
- *eGFR chronic slope was statistically significant with respect to the confirmatory endpoint for the EU*
- *All topline efficacy endpoints favored FILSPARI*
- *FILSPARI was well-tolerated with a consistent safety profile comparable to irbesartan across all clinical trials conducted to date, supporting long-term use*
- *The Company will meet with regulators and expects to submit a supplemental New Drug Application (sNDA) in 1H 2024 for full approval in the U.S.*
- *Company to host conference call and webcast today at 8:30 a.m. ET*

SAN DIEGO, Sept. 21, 2023 (GLOBE NEWSWIRE) -- Travere Therapeutics, Inc. (Nasdaq: TVTX) today announced topline two-year confirmatory secondary endpoint results from the Company's pivotal head-to-head Phase 3 PROTECT Study of FILSPARI ® (sparsentan) in IgA nephropathy (IgAN) versus irbesartan. FILSPARI demonstrated long-term kidney function preservation and achieved a clinically meaningful difference in estimated glomerular filtration rate (eGFR) total and chronic slope versus irbesartan, narrowly missing statistical significance in eGFR total slope while achieving statistical significance in eGFR chronic slope for purposes of regulatory review in the EU. FILSPARI is currently available under accelerated approval in the U.S. The Company will engage with regulators and expects to submit a supplemental New Drug Application (sNDA) in 1H 2024 for full approval in the U.S.

**PROTECT Study Results**

In the PROTECT Study, a total of 404 patients with persistent proteinuria despite active angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) treatment, were randomized 1:1 to receive once daily oral doses of either FILSPARI or irbesartan, the active control. eGFR total and chronic slope are the secondary confirmatory endpoints for the U.S. and the EU, respectively. All topline efficacy endpoints favored FILSPARI as compared to irbesartan.

| | **FILSPARI (N=202)** | **Irbesartan (N=202)** | **Difference (FILSPARI - Irbesartan)** |
|---|---|---|---|
| **eGFR total slope,** mL/min/1.73m$^2$ per year[a] | **-2.9** | **-3.9** | **1.0,** p=0.058 (-0.03, 1.94) |
| **eGFR chronic slope,** mL/min/1.73m$^2$ per year[b] | **-2.7** | **-3.8** | **1.1,** p=0.037 (0.07, 2.12) |
| **UP/C (g/g)** Mean % change from baseline at week 110[c] | **-42.8** | **-4.4** | **GMR: 0.60** (0.50, 0.72) |
| **Absolute change in eGFR** Mean change from baseline at week 110[d] | **-5.8** | **-9.5** | **3.7** (1.45, 5.99) |
| **Absolute change in eGFR** Mean change from baseline at week 114[e] following 4 weeks post treatment (Patients who completed blinded treatment period) | **-6.1** | **-9.0** | **2.9** (0.45, 5.25) |
| **Confirmed 40% Reduction in eGFR, ESRD, or Death during the Study** n (%) | **18** (8.9) | **26** (12.9) | **RR: 0.68** (0.37, 1.24)[f] |

**a LS Means and 95% CI from a random coefficient analysis including available on-treatment eGFR data from Week 6 through Week 110 with multiple imputation; mL/min /1.73m2 per year**

**b LS Means and 95% CI from a random coefficient analysis including available on-treatment eGFR data through Week 110 with multiple imputation; mL/min/1.73m2 per year**

**c Geometric LS Means, Geometric LS Mean Ratio (GMR), and 95% CI from MMRM analysis including on-treatment data through Week 110 with multiple imputation**

**d LS Means and 95% CI from MMRM analysis including on-treatment data through Week 110; mL/min/1.73m2**

**e ANCOVA adjusted for eGFR at baseline; mL/min/1.73m2**

**f Relative risk (RR) of events and 95% CI from Poisson regression model**

A preliminary review of the safety results through 110 weeks of treatment indicates FILSPARI was generally well-tolerated and the overall safety profile in the study has been consistent between treatment groups.

“The confirmatory results of the PROTECT Study demonstrated treatment with FILSPARI resulted in the largest sustained reduction in proteinuria and one of the slowest rates of eGFR decline in a controlled study of IgAN patients, to date. This outcome is incredibly important for IgAN patients, who face the risk of progression to kidney failure in their lifetime. We’re proud of the high bar we’ve set in delivering the only head-to-head study in IgAN, which compares FILSPARI against a maximally tolerated dose of irbesartan,” said Eric Dube, Ph.D., president and CEO of Travere Therapeutics. “Since our accelerated approval, we’ve continued to hear inspiring stories of the impact this medicine is having on people living with IgAN. While eGFR total slope narrowly missed statistical significance, the overall evidence from PROTECT suggests potential long-term benefit of FILSPARI as a foundational treatment for patients with IgAN. FILSPARI has the potential to transform the treatment paradigm in this rare kidney disease, and we look forward to engaging with FDA to discuss our planned sNDA submission.”

“In clinical practice, nephrologists managing IgA nephropathy patients work to reduce proteinuria as much as possible because this leads to a slower rate of decline in kidney function. Our main goal is to avoid the need for dialysis or kidney transplantation. The results of the PROTECT trial clearly show that when compared to an active control of maximally tolerated irbesartan, FILSPARI delivered a rapid and sustained antiproteinuric effect over two years along with a clinically meaningful attenuation in the decline of eGFR that should preserve long-term kidney function in patients with IgAN,” said Brad Rovin, M.D., Medical Director at Ohio State University Center for Clinical Research Management, Director of the Division for Nephrology, and steering committee member for the PROTECT clinical trial. “Because FILSPARI is not an immunosuppressive agent and has a safety profile similar to irbesartan, it has the potential to become long-term foundational therapy for IgAN that could be combined with other therapies as appropriate. This is a promising outcome for patients suffering from IgAN who are at risk for progressive kidney failure.”

The Company will complete a full evaluation of the data from the PROTECT Study and work with the study investigators on future presentations and publications of the results at an upcoming medical meeting and in a peer-reviewed publication.

In August 2022, the European Medicines Agency (EMA) accepted for review the Conditional Marketing Authorization (CMA) application of sparsentan for the treatment of IgAN. Together with its partner CSL Vifor, the Company anticipates a review opinion by the Committee for Medicinal Products for Human Use (CHMP) on the CMA application for sparsentan for the treatment of IgAN in the EU around year-end.

**Conference Call Information**

Travere Therapeutics will host a conference call and webcast today, Thursday, September 21, 2023, at 8:30 a.m. ET to discuss the Phase 3 PROTECT Study results. To participate in the conference call, dial +1 (888) 254-3590 (U.S.) or +1 (323) 994-2093 (International), confirmation code 5916006. The webcast can be accessed on the Investor page of Travere’s website at ir.travere.com/events-presentations. Following the live webcast, an archived version of the call will be available for 30 days on the Company’s website.

**About IgA Nephropathy**

IgA nephropathy (IgAN), also called Berger's disease, is a rare progressive kidney disease characterized by the buildup of immunoglobulin A (IgA), a protein that helps the body fight infections, in the kidneys. The deposits of IgA cause a breakdown of the normal filtering mechanisms in the kidney, leading to blood in the urine (hematuria), protein in the urine (proteinuria) and a progressive loss of kidney function. Other symptoms of IgAN may include swelling (edema) and high blood pressure.

IgAN is the most common type of primary glomerulonephritis worldwide and a leading cause of kidney failure due to glomerular disease. IgAN is estimated to affect up to 150,000 people in the U.S. and is one of the most common glomerular diseases in Europe and Japan.

**About the PROTECT Study**

The PROTECT Study is one of the largest interventional studies to date in IgA nephropathy (IgAN) and the only head-to-head trial in this rare kidney disease. It is a global, randomized, multicenter, double-blind, parallel-arm, active-controlled clinical trial evaluating the safety and efficacy of 400 mg of sparsentan, compared to 300 mg of irbesartan, in 404 patients ages 18 years and up with IgAN and persistent proteinuria despite receiving at least 50% of max label dose and maximally tolerated ACE or ARB therapy. In August 2021, the Company announced the PROTECT Study met its pre-specified interim primary efficacy endpoint with statistical significance. Based on the pre-specified, primary analyses set, after 36 weeks of treatment, patients receiving sparsentan achieved a mean reduction in proteinuria from baseline of 49.8%, compared to a mean reduction in proteinuria from baseline of 15.1% for irbesartan-treated patients ($p<0.0001$). The study’s confirmatory secondary endpoint in the U.S. is eGFR total slope from day 1 to week 110 of treatment. The confirmatory secondary endpoint in the EU is eGFR chronic slope from week 6 to week 110 of treatment, following the initial acute effect of randomized treatment. Following the 110-week blinded treatment period, treatment with study medication is discontinued for 4 weeks -- at this time, the investigator resumes standard of care treatment. Patients that completed the PROTECT double-blind portion of the study on treatment were eligible to participate in the open-label portion of the trial.

**FILSPARI® (sparsentan) U.S. Indication**

FILSPARI is an endothelin and angiotensin II receptor antagonist indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a UPCR ≥1.5 g/g.

This indication is granted under accelerated approval based on reduction in proteinuria. It has not been established whether FILSPARI slows kidney function decline in patients with IgAN. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.

**FILSPARI® (sparsentan) Important Safety Information**

**BOXED WARNING: HEPATOTOXICITY AND EMBRYO-FETAL TOXICITY**
**Because of the risks of hepatotoxicity and birth defects, FILSPARI is available only through a restricted program called the FILSPARI REMS.**

**Under the FILSPARI REMS, prescribers, patients and pharmacies must enroll in the program.**

**Hepatotoxicity**
**Some Endothelin Receptor Antagonists (ERAs) have caused elevations of aminotransferases, hepatotoxicity, and liver failure. In clinical studies, elevations in aminotransferases (ALT or AST) of at least 3-times the Upper Limit of Normal (ULN) have been observed in up to 2.5% of FILSPARI-treated patients, including cases confirmed with rechallenge.**

**Measure transaminases and bilirubin before initiating treatment and monthly for the first 12 months, and then every 3 months during treatment. Interrupt treatment and closely monitor patients who develop aminotransferase elevations more than 3x ULN.**

**FILSPARI should generally be avoided in patients with elevated aminotransferases (>3x ULN) at baseline because monitoring for hepatotoxicity may be more difficult and these patients may be at increased risk for serious hepatotoxicity.**

**Embryo-Fetal Toxicity**
**FILSPARI can cause major birth defects if used by pregnant patients based on animal data. Therefore, pregnancy testing is required before the initiation of treatment, during treatment and one month after discontinuation of treatment with FILSPARI. Patients who can become pregnant must use effective contraception before the initiation of treatment, during treatment, and for one month after discontinuation of treatment with FILSPARI.**

**Contraindications:** FILSPARI is contraindicated in patients who are pregnant. Do not coadminister FILSPARI with angiotensin receptor blockers (ARBs), ERAs, or aliskiren.

**Warnings and Precautions**

Hepatotoxicity: Elevations in ALT or AST of at least 3-fold ULN have been observed. To reduce the risk of potential serious hepatotoxicity, measure serum aminotransferase levels and total bilirubin prior to initiation of treatment, monthly for the first 12 months, then every 3 months during treatment.

Advise patients with symptoms suggesting hepatotoxicity (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching) to immediately stop treatment with FILSPARI and seek medical attention. If aminotransferase levels are abnormal at any time during treatment, interrupt FILSPARI and monitor as recommended.

Consider re-initiation of FILSPARI only when hepatic enzyme levels and bilirubin return to pretreatment values and only in patients who have not experienced clinical symptoms of hepatotoxicity.

Avoid initiation of FILSPARI in patients with elevated aminotransferases (>3x ULN) prior to drug initiation.

**Embryo-Fetal Toxicity:** FILSPARI can cause fetal harm. Advise patients who can become pregnant of the potential risk to a fetus. Obtain a pregnancy test and advise patients who can become pregnant to use effective contraception prior to, during, and one month after discontinuation of FILSPARI treatment.

**FILSPARI REMS:** FILSPARI is available only through a restricted program under a REMS called the FILSPARI REMS.

Important requirements include:

— Prescribers must be certified with the FILSPARI REMS by enrolling and completing training.

— All patients must enroll in the FILSPARI REMS prior to initiating treatment and comply with monitoring requirements.

— Pharmacies that dispense FILSPARI must be certified with the FILSPARI REMS and must dispense only to patients who are authorized to receive FILSPARI.

Further information is available at www.filsparirems.com or 1-833-513-1325.

**Hypotension:** There was a greater incidence of hypotension-associated adverse events, some serious, including dizziness, in patients treated with FILSPARI compared to irbesartan. In patients at risk for hypotension, consider eliminating or adjusting other antihypertensive medications and maintaining appropriate volume status. If hypotension develops, consider a dose reduction or dose interruption of FILSPARI.

**Acute Kidney Injury:** Monitor kidney function periodically. Patients whose kidney function may depend in part on the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing acute kidney injury on FILSPARI. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in kidney function while on FILSPARI.

**Hyperkalemia:** Monitor serum potassium periodically and treat appropriately. Patients with advanced kidney disease, taking concomitant potassium-increasing drugs (e.g., potassium supplements, potassium-sparing diuretics), or using potassium-containing salt substitutes are at increased risk for developing hyperkalemia. Dosage reduction or discontinuation of FILSPARI may be required.

**Fluid Retention:** Fluid retention may occur with ERAs, and has been observed with FILSPARI. If clinically significant fluid retention develops, after evaluation, consider modifying the dose of FILSPARI.

**Most common adverse reactions (5%) with FILSPARI** are peripheral edema, hypotension (including orthostatic hypotension), dizziness, hyperkalemia, and anemia.

**Drug interactions**

- **Renin-Angiotensin System (RAS) Inhibitors and ERAs:** Do not coadminister FILSPARI with angiotensin receptor blockers (ARBs), ERAs, or aliskiren.
- **Strong and Moderate CYP3A Inhibitors:** Avoid concomitant use of FILSPARI with strong CYP3A inhibitors. Monitor blood

pressure, serum potassium, edema, and kidney function regularly when used concomitantly with moderate CYP3A inhibitors.

- **Strong CYP3A Inducers:** Avoid concomitant use with a strong CYP3A inducer.
- **Antacids and Acid Reducing Agents:** Administer FILSPARI 2 hours before or after administration of antacids. Avoid concomitant use of acid reducing agents (histamine H2 receptor antagonist and PPI proton pump inhibitor) with FILSPARI**.**
- **Non-Steroidal Anti-Inflammatory Agents (NSAIDs), Including Selective Cyclooxygenase-2 (COX-2) Inhibitors:** Monitor for signs of worsening renal function.
- **CYP2B6, 2C9, and 2C19 Substrates:** Monitor for efficacy of the concurrently administered CYP2B6, 2C9, and 2C19 substrates and consider dosage adjustment in accordance with the Prescribing Information.
- **P-gp and BCRP Substrates: A**void concomitant use of sensitive substrates of P-gp and BCRP with FILSPARI.
- **Agents Increasing Serum Potassium:** Monitor serum potassium frequently. Concomitant use of FILSPARI with potassium-sparing diuretics, potassium supplements, potassium-containing salt substitutes, or other drugs that raise serum potassium levels may result in hyperkalemia.

**Use in specific populations**

- **Pregnancy / Females and Males of Reproductive Potential:** FILSPARI can cause fetal harm, including birth defects and fetal death, when administered to a pregnant patient and is contraindicated during pregnancy.
    - **Pregnancy Testing / Contraception:** Verify the pregnancy status and effective method of contraception prior to, during, and one month after discontinuation of FILSPARI treatment. The patient should contact their physician immediately for pregnancy testing if onset of menses is delayed or pregnancy is suspected.
- **Lactation:** Advise patients not to breastfeed during treatment with FILSPARI.
- **Hepatic Impairment:** Avoid use of FILSPARI in patients with any hepatic impairment (Child-Pugh class A-C).

**Please see Full Prescribing Information for FILSPARI here.**

**About Travere Therapeutics**

At Travere Therapeutics, we are in rare for life. We are a biopharmaceutical company that comes together every day to help patients, families and caregivers of all backgrounds as they navigate life with a rare disease. On this path, we know the need for treatment options is urgent – that is why our global team works with the rare disease community to identify, develop and deliver life-changing therapies. In pursuit of this mission, we continuously seek to understand the diverse perspectives of rare patients and to courageously forge new paths to make a difference in their lives and provide hope – today and tomorrow. For more information, visit travere.com

**Forward Looking Statements**

*This press release contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995. Without limiting the foregoing, these statements are often identified by the words "anticipate," "believe," "expect," "intend," "may," "might," "objective," "plan," "will" or similar expressions. In addition, expressions of our strategies, intentions or plans are also forward-looking statements. Such forward-looking statements include, but are not limited to, references to: the Company's expectations regarding planned future engagement with FDA regarding the filing of an sNDA for full approval of FILSPARI for patients with IgAN in the U.S. and the timing and outcome thereof; statements regarding the potential long-term benefit of FILSPARI as a foundational treatment for patients with IgAN, the potential to transform the treatment paradigm, and the potential for preservation of long-term kidney function in patients with IgAN; the potential for FILSPARI to be combined with other therapies; statements regarding the Company's further evaluation of the data from the PROTECT Study and work with the study investigators on future presentations and publications; and statements regarding expectations related to the regulatory approval pathway in the US and Europe. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. Among the factors that could cause actual results to differ materially from those indicated in the forward-looking statements are risks and uncertainties associated with the commercial launch of a new product, the regulatory review and approval process, including traditional approval in the United States and the CMA and subsequent variation pathway in the European Union, the Company's business and finances in general, success of its commercial products and the Company's preclinical and clinical stage pipeline. Specifically, the Company faces risks associated with market acceptance of FILSPARI and its other products, including efficacy, safety, price, reimbursement and benefit over competing therapies; the risk that the results of the Phase 3 PROTECT Study of sparsentan in IgAN will not be deemed sufficient by the FDA to to serve as the basis for an sNDA submission for traditional approval of sparsentan; and for each of the Company's programs, risk associated with enrollment of clinical trials for rare diseases and risk that ongoing or planned clinical trials may not succeed or may be delayed for safety, regulatory or other reasons. There is no guarantee that the FDA will grant full approval of sparsentan for IgAN. The Company faces the risk that its cash runway will not extend as far as anticipated and that it will be unable to raise additional funding that may be required to successfully launch FILSPARI in the United States or complete development of any or all of its product candidates, including as a result of macroeconomic conditions; risk relating to the Company's dependence on contractors for clinical drug supply and commercial manufacturing; uncertainties relating to patent protection and exclusivity periods and intellectual property rights of third parties; risks associated with regulatory interactions; risks and uncertainties relating to competitive products, including current and potential future generic competition with certain of the Company's products, and technological changes that may limit demand for the Company's products. The Company also faces additional risks associated with global and macroeconomic conditions, including health epidemics and pandemics, including risks related to potential disruptions to clinical trials, commercialization activity, supply chain, and manufacturing operations. You are cautioned not to place undue reliance on these forward-looking statements as there are important factors that could cause actual results to differ materially from those in forward-looking statements, many of which are beyond our control. The Company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events, or otherwise. Investors are referred to the full discussion of risks and uncertainties, including under the heading "Risk Factors", as included in The Company's most recent Form 10-K, Form 10-Q and other filings with the Securities and Exchange Commission.*

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