Travere Therapeutics Submits Supplemental New Drug Application to the U.S. Food and Drug Administration Seeking Full Approval of FILSPARI® (sparsentan) for the Treatment of IgA Nephropathy (IgAN)

March 11, 2024

Submission is based on 2-year confirmatory results from the Phase 3 PROTECT Study in which FILSPARI demonstrated a significant reduction in proteinuria, preservation of kidney function and a generally well-tolerated safety profile compared with active control irbesartan

SAN DIEGO, March 11, 2024 (GLOBE NEWSWIRE) -- Travere Therapeutics, Inc. (Nasdaq: TVTX) today announced the submission of a supplemental New Drug Application (sNDA) to the U.S. Food and Drug Administration (FDA) for conversion of the existing U.S. accelerated approval of FILSPARI® (sparsentan) in IgA nephropathy (IgAN) to full approval. In February 2023, the FDA granted accelerated approval to FILSPARI as the first and only non-immunosuppressive treatment targeting glomerular injury in the kidney to reduce proteinuria in adults with primary IgAN at risk of rapid disease progression. The sNDA is based on 2-year confirmatory results from the Phase 3 PROTECT Study, the only head-to-head study in IgAN versus an active comparator.

“Since being introduced under accelerated approval, FILSPARI has positively impacted the lives of many people living with IgAN. The submission of the sNDA is an important step toward potentially gaining full approval in IgAN in support of reaching more people living with this devastating rare kidney disease,” said Eric Dube, Ph.D., president and chief executive officer of Travere Therapeutics. “FILSPARI is at the forefront of emerging new treatment options providing hope for a delay in kidney transplant or dialysis. The results from the pivotal Phase 3 PROTECT Study show that by directly targeting glomerular injury in the kidney with FILSPARI, patients can achieve sustained proteinuria reduction and long-term kidney function preservation. We look forward to working with the FDA throughout the upcoming review process.”

FILSPARI is a once-daily, oral medication that directly targets glomerular injury in the kidney by blocking two critical pathways of IgAN disease progression (endothelin-1 and angiotensin II). FILSPARI is also the first and only non-immunosuppressive therapy approved for the treatment of this rare kidney disease. The sNDA submission is supported by results from the Phase 3 PROTECT Study that showed that FILSPARI demonstrated long-term kidney function preservation and achieved a significant reduction in proteinuria and a clinically meaningful difference in eGFR slope versus an active comparator.

The FDA has 60 days from the receipt of the application to determine whether to accept it for review. The Company expects to receive notice regarding the acceptance for review of the sNDA submission as well as the timeline for sNDA review from the FDA in the second quarter of 2024. In addition to the sNDA submission to the FDA, the Company and its European commercial partner CSL Vifor recently announced that the European Medicines Agency’s (EMA) Committee for Medicinal Products for Human Use (CHMP) has recommended approval of the conditional marketing authorization (CMA) for sparsentan for the treatment of IgA nephropathy (IgAN) in Europe. A decision by the European Commission is expected in the second quarter of 2024. If approved, sparsentan would receive a CMA in all member states of the European Union, as well as in Iceland, Liechtenstein, and Norway.

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 estimated glomerular filtration rate (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 was discontinued for 4 weeks -- at this time, the investigator resumed standard of care treatment.
In September 2023, the Company announced topline two-year confirmatory secondary endpoint results from the PROTECT Study of sparsentan in IgAN. Sparsentan demonstrated long-term kidney function preservation and achieved a clinically meaningful difference in 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. Patients who completed the PROTECT double-blind portion of the study on treatment were eligible to participate in the open-label extension of the trial.

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

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:** Avoid 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.

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 “on-track,” “positioned,” “look forward to,” “will,” “would,” “may,” “might,” “believes,” “anticipates,” “plans,” “expects,” “intends,” “potential,” 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: statements and expectations regarding the FDA’s potential acceptance for filing of the sNDA submission for FILSPARI in IgAN and the anticipated timeline and outcome of the FDA’s review of the sNDA; statements regarding the potential conditional marketing authorization of sparsentan for the treatment of IgAN in the European Union, Iceland, Liechtenstein and Norway and the anticipated timing thereof, including the potential timing and outcome of the European Commission’s decision; and the potential for emerging new treatment options for IgAN that have the potential to provide hope for a delay in kidney transplant or a dialysis. 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 regulatory review and approval process, as well as risks and uncertainties associated with the Company’s business and finances in general, the success of its commercial products and risks and uncertainties associated with the Company’s preclinical and clinical stage pipeline. Specifically, the Company faces risks associated with market acceptance of its commercial products including efficacy, safety, price, reimbursement, and benefit over competing therapies, as well as risks associated with the successful development and execution of commercial strategies for such products, including FILSPARI. The risks and uncertainties the Company faces with respect to its preclinical and clinical stage pipeline include risk that the Company’s clinical candidates will not be found to be safe or effective and that current or anticipated future clinical trials

will not proceed as planned. Specifically, the Company faces risks related to the timing and potential outcome of the FDA's potential acceptance for filing and review of the sNDA submission for full approval of FILSPARI in IgAN, and the timing and potential outcome of the European Commission's decision regarding conditional marketing authorization of sparsentan for IgAN. There is no guarantee that the FDA will accept the sNDA submission for filing, that the European Commission will grant conditional marketing authorization of sparsentan for IgAN, or that regulators will grant full approval of sparsentan for IgAN. The Company also faces the risk that it will be unable to raise additional funding that may be required to complete development of any or all of its product candidates, including as a result of macroeconomic conditions; risks 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; and 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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