Travere Therapeutics Announces FDA Accelerated Approval of FILSPARI™ (sparsentan), the First and Only Non-immunosuppressive Therapy for the Reduction of Proteinuria in IgA Nephropathy

February 17, 2023

First single molecule Dual Endothelin Angiotensin Receptor Antagonist (DEARA) approved for use in patients with IgA nephropathy (IgAN)

Interim results from the ongoing Phase 3 PROTECT head-to-head trial demonstrated a rapid, sustained and clinically meaningful reduction in proteinuria vs. active control, irbesartan

Company to host conference call February 17, 2023 4:30pm ET

SAN DIEGO, Feb. 17, 2023 (GLOBE NEWSWIRE) -- Travere Therapeutics, Inc. (Nasdaq: TVTX) today announced that the U.S. Food and Drug Administration (FDA) has granted accelerated approval to FILSPARI™ (sparsentan) to reduce proteinuria in adults with primary IgAN at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (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. The continued approval of FILSPARI may be contingent upon confirmation of a clinical benefit in the ongoing Phase 3 PROTECT Study, which is designed to demonstrate whether FILSPARI slows kidney function decline. Topline results from the two-year confirmatory endpoints in the PROTECT Study are expected in the fourth quarter of 2023 and are intended to support traditional approval of FILSPARI.

FILSPARI, a once-daily oral medication is designed to selectively target two critical pathways in the disease progression of IgAN (endothelin-1 and angiotensin II), and is the first and only non-immunosuppressive therapy approved for the treatment of this condition. IgAN is a rare kidney disease (RKD) and a leading cause of kidney failure due to glomerular disease, affecting up to 150,000 people in the U.S., with approximately 30,000 to 50,000 of such patients estimated to be addressable under the indication approved via accelerated approval. The Company expects FILSPARI to be available beginning the week of February 27, 2023, and will be providing a comprehensive patient support program throughout the patient's treatment journey.

"The accelerated approval of FILSPARI is a significant milestone on our path to advancing a transformative treatment for the IgA nephropathy community," said Eric Dube, Ph.D., president and chief executive officer, Travere Therapeutics. "As a first-of-its-kind, non-immunosuppressive therapy, we believe FILSPARI has the potential to ultimately become the new standard of care for IgA nephropathy and offer hope to those living with this condition who until now have had few treatment options. We are grateful to the patients, caregivers, clinical trial investigators, healthcare providers, and advocates who have worked alongside us to develop this innovative first-in-class therapy."

"Today's approval of FILSPARI sets the stage for a new standard of care for IgA nephropathy patients. A high proportion of individuals diagnosed with this disease do not sufficiently respond to the historical standard treatment, which has been therapies that are not indicated for IgA nephropathy. These treatments include hypertension drugs such as angiotensin-receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors and systemic glucocorticoids. As a result, many patients have struggled to manage their disease and have progressed more quickly to kidney failure," said Dr. Brad Rovin, MD, 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. "The approval of this innovative treatment is founded in data from the largest head-to-head Phase 3 clinical trial in IgA nephropathy. It is exciting to see that adult patients who are at risk of rapid disease progression, many of whom have waited a very long time for a treatment like this, now have hope for a better future."

The approval of FILSPARI, granted under the FDA's accelerated approval pathway, is based on clinically meaningful and statistically significant improvements in proteinuria compared to an active comparator in the pivotal and ongoing Phase 3 PROTECT Study, the largest head-to-head interventional study to date in IgAN. The PROTECT Study is a global, randomized, multicenter, double-blind, active-controlled clinical trial evaluating the safety and efficacy of 400 mg of FILSPARI, compared to 300 mg of irbesartan, in 404 patients ages 18 years and up with IgAN and persistent proteinuria despite maximal tolerated ACE or ARB therapy.

In August 2021, the Company announced positive topline interim results that were based on the pre-specified, primary analyses set which showed that after 36 weeks of treatment, patients receiving FILSPARI 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 ($p<0.0001$). Per request from the FDA, the efficacy data contained in the FDA-approved label is a post-hoc sensitivity analysis that evaluates the first 281 randomized patients, a subset of the full trial population. The mean reduction in proteinuria from baseline in the post-hoc sensitivity analysis is 45% for FILSPARI versus 15% for the active control, irbesartan. Both the pre-specified and post-hoc sensitivity analyses have demonstrated that FILSPARI achieves a rapid and sustained reduction in proteinuria, with statistically significant and clinically meaningful improvement compared to the active comparator irbesartan. Per the study protocol, patients continue in a blinded manner in the PROTECT Study to fully assess the treatment effect on eGFR slope over 110 weeks in the confirmatory endpoint analysis. Results from the confirmatory endpoint analysis are expected in the fourth quarter of 2023.

Results from the interim assessment in the PROTECT Study showed that FILSPARI was well tolerated with a clearly defined safety profile that has been consistent across all clinical trials conducted to date. In PROTECT, the most common adverse reactions (≥ 5%) are peripheral edema, hypotension (including orthostatic hypotension), dizziness, hyperkalemia, and anemia. Because of the risks of liver injury and birth defects, FILSPARI is available only through a Risk Evaluation and Mitigation Strategy (REMS) approved by the FDA.

Bonnie Schneider, executive director and co-founder of the IgA Nephropathy Foundation said, "For decades people living with IgA nephropathy have had limited treatment options while facing a progression toward kidney failure. Today is a day of celebration for the RKD community, for our patients, and their families."

"IgA nephropathy is associated with depression, fatigue, loss of social and work opportunities and anxiety about the need for dialysis or transplant. The disease often manifests in adults in their 20s or 30s – a time when people are focused on building livelihoods and families," said Kelly Helm, executive director of patient engagement at NephCure. "We are thrilled that today's FDA accelerated approval of FILSPARI brings forward a new and innovative treatment option for many people living with IgA nephropathy."

Travere Therapeutics has established Travere TotalCare™ to provide a comprehensive patient support program to enable a smooth experience for patients, their caregivers and healthcare providers. This program provides services, assistance and resources that will help patients understand IgAN, manage the insurance process, fill their prescriptions and initiate treatment. Patients or providers can call 833-FILSPARI (833-345-7727) to learn more.

In the second half of 2023, the Company together with its collaborator CSL Vifor, anticipates a review decision by the European Medicines Agency (EMA) on the potential approval of the Conditional Marketing Authorization (CMA) application for sparsentan for the treatment of IgAN in Europe.

In the second quarter of 2023, the Company expects to report topline results from the two-year confirmatory endpoints in the ongoing Phase 3 DUPLEX Study of sparsentan in focal segmental glomerulosclerosis (FSGS). Pending supportive data, the Company anticipates submitting a supplemental NDA for traditional approval for an FSGS indication in the second half of 2023 and a subsequent variation to the CMA of sparsentan for the treatment of patients with FSGS in Europe is targeted for submission by the end of 2023. Sparsentan has been granted Orphan Drug Designation for the treatment of IgAN and FSGS in the U.S. and Europe.

Conference call information

Travere Therapeutics will host a conference call and webcast today, Friday, February 17, 2023 at 4:30 p.m. ET to discuss the FDA accelerated approval and launch of FILSPARI. To participate in the conference call, dial +1 (888) 204-4368 (U.S.) or +1 (323) 994-2093 (International), confirmation code 6927185. 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 FILSPARI (sparsentan)

FILSPARI (sparsentan) is a once-daily, oral medication designed to selectively target two critical pathways in the disease progression of IgAN (endothelin-1 and angiotensin II) and is the first and only non-immunosuppressive therapy approved for the treatment of this condition. FILSPARI is a prescription medicine indicated to reduce proteinuria in adults with primary IgAN at risk of rapid disease progression, generally a UPCR ≥1.5 g/g.

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.

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

About the PROTECT Study

The ongoing PROTECT Study is one of the largest interventional studies to date in IgAN. It is a global, randomized, multicenter, double-blind, parallel-arm, active-controlled clinical trial evaluating the safety and efficacy of 400mg of sparsentan, compared to 300mg of irbesartan, in 404 patients ages 18 years and up with IgAN and persistent proteinuria despite available 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 percent, compared to a mean reduction in proteinuria from baseline of 15.1 percent for irbesartan-treated patients ($p<0.0001$). The Company believes that preliminary eGFR data available at the time of the interim analysis are indicative of a potential clinically meaningful treatment effect after two years of treatment. Preliminary results at the time of the interim assessment suggested that sparsentan had been generally well-tolerated to date in the study and consistent with its overall observed safety profile. The PROTECT Study is fully enrolled and is scheduled to continue as planned on a blinded basis to assess the treatment effect on eGFR slope over 110 weeks in the confirmatory endpoint analysis. Topline results from the confirmatory endpoint analysis are expected in the fourth quarter of 2023.

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 when FILSPARI will be available; the expected timing for reporting topline results from the confirmatory endpoint analysis of the PROTECT Study; the Company’s belief that preliminary eGFR data from the PROTECT Study available at the time of the interim analysis are indicative of a potential clinically meaningful treatment effect after two years of treatment; the potential traditional regulatory approval of sparsentan for IgAN; the estimated addressable U.S. patient population for FILSPARI under the indication approved via accelerated approval; the potential of FILSPARI to ultimately become the new standard of care for IgAN; the anticipated review decision by the EMA on the potential approval of the CMA application for sparsentan for the treatment of IgAN, and the timing thereof; the timing for reporting toplines results from the confirmatory endpoints in the ongoing DUPLEX Study in FSGS; and the Company’s plan to submit a supplemental NDA for traditional approval for FSGS in the second half of 2023 and a subsequent variation to the CMA of sparsentan for the treatment of FSGS in Europe by the end of 2023, pending supportive data. 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 both traditional approval and the accelerated approval pathway in the United States and the CMA 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 commercial products, including efficacy, safety, price, reimbursement and benefit over competing therapies; the risk that the confirmatory endpoint analysis from the Phase 3 PROTECT Study will not serve as a basis for traditional approval of FILSPARI; the risk that the Phase 3 DUPLEX Study of sparsentan in FSGS will not demonstrate that sparsentan is safe or effective or serve as the basis for traditional approval of sparsentan; the risk that sparsentan for FSGS will not be approved for efficacy, safety, regulatory or other reasons; 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 traditional approval of sparsentan for IgAN or FSGS. The Company faces risk 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; 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 faces additional risks associated with the potential

impacts that a resurgence of COVID-19 or other health epidemic or pandemic may have on its business, including, but not limited to the Company's ability to continue its ongoing development activities and clinical trials, the timing of such clinical trials and the release of data from those trials, the Company's and its suppliers' ability to successfully manufacture its commercial products and product candidates, and the market for and sales of its commercial products. 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 as included under the "Risk Factors" heading of the Company's Quarterly Report on Form 10-Q for the quarter ended September 30, 2022, as filed with the Securities and Exchange Commission ("SEC") on October 27, 2022, and other filings with the SEC.

A photo accompanying this announcement is available at https://www.globenewswire.com/NewsRoom/AttachmentNg/21920774-d9c9-4c88-9a02-3a33a53714e8

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