# Travere Therapeutics Announces Late-Breaking Data from Phase 3 Studies of Sparsentan in IgAN and FSGS Published in The Lancet and The NEJM Respectively and Presented at the American Society of Nephrology (ASN) Kidney Week 2023

November 3, 2023

*Two-year results from both PROTECT and DUPLEX pivotal Phase 3 studies demonstrate treatment with sparsentan has the potential to preserve kidney function and significantly delay time to kidney failure, suggesting long-term benefits in IgAN and FSGS*

*In PROTECT, the only head-to-head study conducted to date in IgAN, FILSPARI® (sparsentan) showed one of the slowest rates of kidney function decline in IgAN trials, consistent treatment effects across baseline eGFR and proteinuria, and higher rates of complete remission compared to maximally tolerated dose of irbesartan through 110 weeks of treatment*

*In DUPLEX, the largest interventional study in FSGS and only study against a maximally dosed active comparator, sparsentan delivered a clinically meaningful benefit at 108 weeks with significant proteinuria reduction, higher rates of partial and complete remission, and lower rates of end-stage kidney disease*

*Sparsentan was well tolerated with a safety profile comparable to the maximally tolerated dose of irbesartan in both Phase 3 studies, including no drug-induced liver injury or fluid overload*

SAN DIEGO, Nov. 03, 2023 (GLOBE NEWSWIRE) -- Travere Therapeutics, Inc. (Nasdaq: TVTX) today announced additional data from two pivotal clinical studies demonstrating sparsentan has the potential to preserve kidney function and significantly delay time to kidney failure compared to an active comparator, suggesting long-term benefits in IgA nephropathy (IgAN) and focal segmental glomerulosclerosis (FSGS). Data from the Phase 3 PROTECT and DUPLEX Studies were presented as late-breaking oral presentations at the American Society of Nephrology (ASN) Kidney Week 2023 and simultaneously published in *The Lancet* (PROTECT) and *The New England Journal of Medicine* (DUPLEX).

"We're proud to have set the bar very high in delivering clinically meaningful data from two of the most rigorous Phase 3 clinical trials to date in IgAN and FSGS and to now share these two-year data in prestigious peer-reviewed journals and at ASN Kidney Week," said Jula Inrig, M.D., chief medical officer of Travere Therapeutics. "These data from PROTECT suggest that FILSPARI has the potential to significantly delay time to kidney failure, which based on recently published data is projected to be an additional eight years versus being treated with standard of care."

**Key Findings from the Two-Year PROTECT Study in IgAN:**

- Treatment with FILSPARI resulted in one of the slowest rates of kidney function decline in an IgAN trial of its kind (-2.7 and -2.9 ml/min/1.73m$^2$/year with chronic and total eGFR slope, respectively).
- The absolute overall change in kidney function from baseline to the end of the study for patients treated with FILSPARI was -5.8 mL/min/1.73m$^2$ compared to -9.5 mL/min/1.73m$^2$ with irbesartan. This translates into a 3.7 mL/min/1.73m$^2$ higher eGFR at two years with FILSPARI compared to irbesartan. This beneficial effect on preserving kidney function was durable post washout.
- Treatment effects on eGFR slope were consistent across baseline eGFR and proteinuria, supporting the potential for FILSPARI as a foundational treatment option across different stages of disease.
- When imbalances between treatment arms were factored into pre-specified eGFR analyses (early treatment discontinuations and higher rates of rescue immunosuppression, both of which occurred more in the irbesartan arm) the beneficial effects of FILSPARI on kidney function preservation were strengthened.
- Treatment with FILSPARI demonstrated lower rates of the composite endpoint of 40% decline in eGFR, kidney failure or death compared to irbesartan.
- Treatment with FILSPARI resulted in the largest magnitude of sustained reduction in proteinuria shown in a pivotal trial over two years with FILSPARI-treated patients achieving a mean reduction in proteinuria from baseline of 43% compared to 4% for irbesartan-treated patients.
- More patients treated with FILSPARI achieved complete remission of proteinuria of less than 0.3 grams compared to those treated with irbesartan (31% vs 11%).
- FILSPARI was well-tolerated with a safety profile that was consistent across all clinical trials conducted to date and comparable to the active control, irbesartan, including no drug-induced liver injury and no fluid overload.

"The totality of data from the PROTECT study demonstrates FILSPARI is effective, safe and has an important place in the IgAN treatment landscape as a long-term foundational therapy," 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.

**Key Findings from the Two-Year DUPLEX Study in FSGS:**

- Treatment with sparsentan demonstrated a clinically meaningful and durable reduction in proteinuria, with FSGS patients achieving a 50% reduction from baseline, compared to a 32% reduction with the active control irbesartan.
- Sparsentan showed a consistent and sustained achievement of complete remission of proteinuria in 18.5% of patients on sparsentan vs. 7.5% for irbesartan.
- The combined hard endpoints of confirmed 50% reduction in eGFR, end-stage renal disease or death, trended in favor of sparsentan with fewer patients progressing to kidney failure.
- Sparsentan was well-tolerated with a safety profile that was consistent across all clinical trials conducted to date and comparable to the active control, irbesartan, including no drug-induced liver injury and no fluid overload.

"FSGS is an incredibly complex and heterogeneous rare kidney disease that can be difficult to study and currently has no approved pharmacologic treatment options. In the DUPLEX Study, which is the largest study in FSGS ever conducted, we are seeing for the first time a non-immunosuppressive medicine making a clinically meaningful impact in patients' lives by reducing proteinuria, a proven indicator of kidney damage, by 50%," said Michelle N. Rheault, M.D., Director at the Division of Pediatric Nephrology, University of Minnesota Medical School and steering committee member for the DUPLEX clinical trial.

Additional abstracts presented at Kidney Week 2023 reinforce the potential for FILSPARI to play an important foundational role in the IgAN treatment landscape, including in exploring the potential combination with sodium-glucose cotransporter-2 (SGLT2) inhibitors, and provide insights into patient quality of life and the impact of proteinuria on kidney survival.

**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. FILSPARI 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 FSGS**

Focal segmental glomerulosclerosis (FSGS) is a rare proteinuric kidney disorder in both children and adults that is estimated to affect more than 40,000 patients in the U.S. with similar prevalence in Europe. The disorder is defined by progressive scarring of the kidney and often leads to kidney failure. FSGS is characterized by proteinuria, where protein leaks into the urine due to a breakdown of the normal filtration mechanism in the kidney. Once in the urine, protein is considered to be toxic to other parts of the kidney, especially the tubules, and is believed to contribute to further disease progression. Other common symptoms include swelling in parts of the body, known as edema, as well as low blood albumin levels, abnormal lipid profiles and hypertension. There is currently no approved pharmacologic indicated for the treatment of FSGS.

**About the DUPLEX Study**

The DUPLEX Study is the largest interventional study to date in FSGS. It is a global, randomized, multicenter, double-blind, parallel-arm, active-controlled Phase 3 clinical trial assessing the efficacy and safety of sparsentan in 371 patients ages 8 to 75 years with primary FSGS. After a two-week washout period, patients are randomized 1:1 to receive either sparsentan or irbesartan, the active control, and subsequently dose titrated to the maximum dose of 800 mg of sparsentan or 300 mg of irbesartan, as tolerated. In February 2021, the Company announced that the pivotal Phase 3 DUPLEX Study of sparsentan in FSGS achieved its pre-specified interim FSGS partial remission of proteinuria (FPRE) endpoint with statistical significance. FPRE is a clinically meaningful endpoint defined as urine protein-to-creatinine ratio (UP/C) ≤1.5 g/g and a >40 percent reduction in UP/C from baseline. After 36 weeks of treatment, 42.0 percent of patients receiving sparsentan achieved FPRE, compared to 26.0 percent of irbesartan-treated patients ($p=0.0094$). The study's primary efficacy endpoint in the U.S. is the eGFR total slope from day 1 to week 108 of treatment. The primary efficacy endpoint in Europe is the eGFR chronic slope, from week 6 to week 108 of treatment, following the initial acute effect of randomized treatment. In May 2023, the Company announced topline primary efficacy results from the DUPLEX Study of sparsentan in FSGS. The DUPLEX Study did not

achieve the primary efficacy eGFR slope endpoint over 108 weeks of treatment. Secondary and topline exploratory endpoints trended favorably for sparsentan. Treatment with sparsentan resulted in a reduction of proteinuria that was sustained through 108 weeks of treatment. Results from the two-year analysis demonstrated that sparsentan was well-tolerated and has shown a comparable safety profile to irbesartan. Patients who completed the DUPLEX double-blind portion of the study on treatment were eligible to participate in the open-label extension of the trial. Sparsentan is not FDA-approved for treatment of FSGS.

**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: 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.**

**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 potential for FILSPARI (sparsentan) to play an important foundational role in the IgAN treatment landscape and the exploration of the potential combination of FILSPARI with SGLT2 inhibitors, references to data on the long-term efficacy and tolerability of FILSPARI in IgAN and of sparsentan in FSGS, references to the PROTECT and DUPLEX trials, and references to potential long-term benefits and the potential magnitude thereof, including preservation of kidney function and delay of time to kidney failure, including projections of the period of potential delay based on the models derived from published 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 regulatory review and approval process, risks associated with enrollment of clinical trials for rare diseases, and risks that ongoing or planned clinical trials may not succeed or may be delayed for safety, regulatory or other reasons. The Company faces risks related to the commercial launch of a new product; risks associated with market acceptance of FILSPARI and other current and future 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 serve as the basis for an sNDA submission for traditional approval of sparsentan; and the risk that the results from the Phase 3 DUPLEX study of sparsentan in FSGS will not serve as a basis for a regulatory submission for approval of sparsentan for FSGS. There is no guarantee that regulators will grant full approval of sparsentan for IgAN or FSGS. 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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