Travere Therapeutics Announces Topline Results from Two-Year Primary Efficacy Endpoint in Pivotal Phase 3 DUPLEX Study of Sparsentan in Focal Segmental Glomerulosclerosis

May 1, 2023

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

Sparsentan was well-tolerated with a consistent safety profile across all clinical trials conducted to date and comparable to irbesartan

Company to host conference call and webcast today at 4:30pm ET

SAN DIEGO, May 01, 2023 (GLOBE NEWSWIRE) -- Travere Therapeutics, Inc. (Nasdaq: TVTX) today announced topline primary efficacy results from the pivotal Phase 3 DUPLEX Study of sparsentan, a Dual Endothelin Angiotensin Receptor Antagonist (DEARA), in focal segmental glomerulosclerosis (FSGS). At the end of the 108-week double-blind period, sparsentan was observed to have a 0.3 mL/min/1.73m^2 per year (95% CI: -1.74, 2.41) favorable difference on eGFR total slope and a 0.9 mL/min/1.73m^2 per year (95% CI: -1.27, 3.04) favorable difference on eGFR chronic slope compared to the active control irbesartan, which was not statistically significant. After 108 weeks of treatment, sparsentan achieved a mean reduction in proteinuria from baseline of 50%, compared to 32% for irbesartan. Results from the two-year analysis demonstrated that sparsentan was well-tolerated and has shown a comparable safety profile to irbesartan.

The Company will engage with regulators to explore a potential path forward for a supplemental New Drug Application (sNDA) in the U.S. Together with its collaborator CSL Vifor, the Company also plans to engage with the European Medicines Agency (EMA) to determine the potential for a subsequent variation to the Conditional Marketing Authorization (CMA) of sparsentan for the treatment of FSGS, subject to a review decision on the pending application for the CMA of sparsentan in IgA nephropathy.

“FSGS is a leading cause of kidney failure with no medicines currently approved for the condition. For the last several years we have been leading development efforts in this area which has culminated in the largest interventional study conducted to-date in FSGS, and the only one comparing a candidate against an active control,” said Eric Dube, Ph.D., president and chief executive officer of Travere Therapeutics. “We are disappointed that we did not achieve the primary efficacy endpoint in this study, but we did see results that trended favorably for sparsentan that we are further exploring to determine a potential path forward in FSGS. We are grateful for the patients, their caregivers, the investigators, clinical staff, the patient advocacy groups and our entire team at Travere who came together to support the DUPLEX Study.”

FSGS is a rare kidney disease (RKD) defined by progressive scarring of the kidney resulting in proteinuria and rapid decline in kidney function. It is a leading cause of kidney failure due to glomerular disease. FSGS is estimated to affect more than 40,000 patients in the U.S. with similar prevalence in Europe.

“FSGS is a devastating, progressive and complex rare kidney disease. As such, FSGS is one of the most difficult glomerular diseases to study and the results from our DUPLEX Study reinforce this and further highlight the significant unmet need that exists,” said Dr. Jula Inrig, M.D., chief medical officer at Travere Therapeutics. “We believe the results from DUPLEX will be instrumental in helping to inform the medical community’s understanding of FSGS, and we are committed to further exploring our data to understand the potential role sparsentan could play in the treatment of FSGS.”

In the DUPLEX Study, a total of 371 patients were randomized 1:1 to receive either sparsentan or irbesartan, the active control.

eGFR Primary Efficacy Endpoints:

- **Total slope** (primary endpoint in US)**:** From day one to week 108, the difference in eGFR total slope was 0.3 mL/min /1.73m^2 per year in favor of sparsentan (-5.4 mL/min per 1.73 m^2 per year; 95% CI: -6.89, -3.93) versus the active control irbesartan (-5.7 mL/min per 1.73 m^2 per year; 95% CI: -7.20, -4.29), p=0.7491.
- **Chronic slope** (primary endpoint in Europe): From week 6 to week 108 of treatment, following the initial acute effect of randomized treatment, the difference in eGFR chronic slope was 0.9 mL/min/1.73m^2 per year in favor of sparsentan (-4.8 mL/min per 1.73 m^2 per year; 95% CI: -6.34, -3.27) versus the active control irbesartan (-5.7 mL/min per 1.73 m^2 per year; 95% CI:-7.20, -4.18), p=0.4203.

The secondary and topline exploratory endpoints, including renal outcomes, trended favorably for sparsentan in the study.

Proteinuria Two-Year Exploratory Endpoints:

- **Urine protein-to-creatinine ratio** (**UP/C):** After 108 weeks of treatment, the change from baseline UP/C was 50% for sparsentan versus 32% for irbesartan.
- **FSGS partial remission of proteinuria endpoint (FPRE):** At week 108, 38% of patients on sparsentan achieved FPRE compared with 23% on irbesartan.

- **Complete remission:**18% of patients on sparsentan versus 7% on irbesartan achieved complete remission of proteinuria (UP/C <0.3 g/g) at any time during the double-blind period.

A preliminary review of the safety results through 108 weeks of treatment indicate sparsentan has been generally well-tolerated and the overall safety profile in the study to date has been generally consistent between treatment groups.

The Company intends to complete a full evaluation of the data from the DUPLEX Study and work with study investigators on future presentations and publication of the results at an upcoming medical meeting and/or in a peer-reviewed publication.

Conference call information

Travere Therapeutics will host a conference call and webcast today, Monday, May 1, 2023 at 4:30 p.m. ET to discuss the DUPLEX Study results. To participate in the conference call, dial +1 (888) 394-8218 (U.S.) or +1 (323) 994-2093 (International), confirmation code 8592337. 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 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 US 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 ongoing 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). Preliminary results from the interim analysis suggest that at the time of the interim assessment, sparsentan had been generally well-tolerated and shown a comparable safety profile to irbesartan. The study's primary efficacy endpoint in the US 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. Patients that completed the DUPLEX 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:** 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

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”, "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: the efficacy, safety and tolerability profile of sparsentan based on the topline data from the DUPLEX Study which is based on a preliminary analysis of the data and subject to more comprehensive analyses, including with respect to the secondary and topline exploratory endpoints, including renal outcomes; the Company’s plan and timing for engaging with regulators to explore a potential path for a regulatory submission of sparsentan for FSGS; expectations regarding the ability to present the results from the DUPLEX Study at an upcoming medical meeting and/or in a peer-reviewed journal; the potential ability to submit a supplemental NDA for sparsentan for FSGS in the U.S. and the potential for a submission for a subsequent variation to the Conditional Marketing Authorization (CMA) of sparsentan for the treatment of FSGS in Europe, subject to a review decision on the pending application for CMA of sparsentan in IgA nephropathy; the Company’s belief that the results from DUPLEX will be instrumental in helping to inform the medical community’s understanding of FSGS, and its plan to further explore the data to understand the potential role sparsentan could play in the treatment of FSGS. 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, including the traditional and Subpart H accelerated approval pathways in the United States and the CMA pathway in the European Union, as well as risks and uncertainties associated with the Company’s business and finances in general, 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 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; the risk that the Phase 3 PROTECT Study of sparsentan in IgAN will not demonstrate that sparsentan is safe or effective or serve as the basis for further approval of sparsentan; the risk that sparsentan will not be approved further 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 or abandoned for safety, regulatory, program assessment or other reasons. There is no guarantee that the Company will be able to establish a pathway to a potential submission of sparsentan for FSGS based on the results from the DUPLEX Study, that the FDA and/or EMA will support an application for sparsentan in FSGS, or that sparsentan will be approved for FSGS. The Company faces 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; 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 as included under the heading “Risk Factors” in the Company's Annual Report on Form 10-K for the year ended December 31, 2022, as filed with the Securities and Exchange Commission on February 23, 2023.

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