BIOTUESDAYS
by Kilmer Lucas

XORTX awaiting key clinical milestones in treating progressive kidney diseases

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XORTX Therapeutics (CSE:XRX; OTCQB:XRTXF) is awaiting several key milestones during the next few months as it works to redefine how progressive kidney disease is treated.

Allen Davidoff, Co-Founder, President and CEO

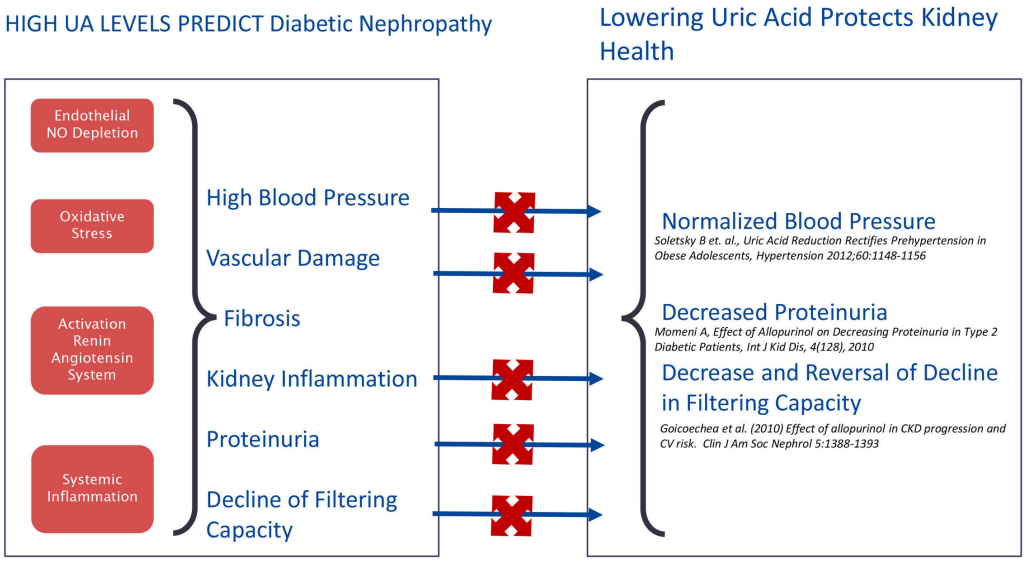
"Our two lead programs are targeting uric acid lowering, which has been shown to have an important clinical effect in this disease," Allen Davidoff, co-founder, president and CEO, says in an interview with BioTuesdays.

"We have a strong IP portfolio and well established proof-of-concept for our XRx-008 to treat autosomal dominant polycystic kidney disease (ADPKD), an orphan market, and XRx-221 for Type 2 diabetic nephropathy (T2DN), a large market," he adds.

In August, XORTX expects to receive top line results from a Phase 2a study of XRx-221 in T2DN, under a co-development deal with Japan's Teijin Pharma. XORTX also is expecting a European patent for its diabetic nephropathy program and is readying strategic discussions.

ADPKD is a life-threatening genetic disease, where fluid-filled cysts develop and enlarge in both kidneys, eventually leading to kidney failure. More than 50% of people with ADPKD will develop kidney failure by age 50. Once a person has kidney failure, dialysis or a transplant is the only option.

Dr. Davidoff explains that elevated uric acid is a bad actor in kidney disease. There is a substantial body of independent Phase 2 clinical trial evidence that suggests high levels of uric acid can lead to high blood pressure, vascular damage, kidney inflammation, fibrosis, decline in the kidney's filtering capacity and high levels of protein in urine.



Uric Acid (UA): a Bad Actor in Kidney Disease

A peer-reviewed study published in BMC Nephrology in 2014 found that reducing uric acid levels in ADPKD patients increased kidney-filtering capacity by some 175% after one year, effectively reversing the course of the disease.

XORTX's patent portfolio covering uric acid-lowering agents used in progressive kidney disease extends to as late as 2037.

Dr. Davidoff says that recent discussions with the FDA about XORTX's orphan drug program in ADPKD resulted in an accelerated clinical development program, with guidance that the program could advance to a pivotal Phase 3 registration trial under a special protocol approval (SPA).

"The FDA discussion that clarified this approach, effectively halved the development time and cost for the ADPKD program and accelerated the opportunity to have a marketed drug for ADPKD patients within four years," he adds.

Dr. Davidoff also indicates that more than 10 international specialty pharma companies have reached out to XORTX, expressing interest in licensing the ADPKD program a variety of jurisdictions.

XORTX's XRx-008 drug candidate is a proprietary formulation of Oxypurinol, which already has an established safety and efficacy data. "Our formulation of XRx-008 has three times greater bioavailability than Oxypurinol alone, enabling increased oral dosing ranges, while its improved tolerability increases compliance and supports chronic dosing," he contends.

There are some 120,000 ADPKD patients in the U.S. and, at a projected revenue per patient of $30,000 a year, XRx-008 has the potential to generate annual peak sales of nearly $2-billion in the US alone.

At the beginning of 2020, XORTX plans to conduct a one-month bioavailability study with XRx-008, ahead of initiating a pivotal study under a SPA in the first half of 2020. Data would read out in 2022.

"If we can demonstrate slowing or reversing the decline in the rate of kidney filtration by 35% to 40%, we would reach the FDA's approval threshold," Dr. Davidoff suggests. Currently published pilot trials in ADPKD and T2DN both show clinically meaningful benefit for individuals far in excess of this threshold.

XORTX intends to file an NDA for XRx-008 under accelerated review at the beginning of 2023 and achieve marketing approval one year later.

The company's second program, to slow or even reverse progression of diabetic kidney disease, is in a co-development deal with Teijin Pharma that grants XORTX exclusive global rights to XRx-221.

"We are indeed honored that Teijin has agreed to allow the XORTX Therapeutics' development team act as the custodian for this next generation uric acid lowering drug," Dr. Davidoff says. The agreement provides exclusive global rights to develop the drug for kidney diseases, including T2DN. XORTX views this milestone as a validation of the expertise and patent protection that XORTX provides.

Dr. Davidoff says that following Teijin's ongoing Phase 2a diabetic kidney study, which reads out in August, the company hopes to begin a Phase 2b clinical trial with some 400 T2DN patients to demonstrate the drug candidate's ability to improve glomerular filtration rate – XORTX's preferred, and an FDA approvable endpoint.

"This potent, next generation uric acid-lowering drug candidate has the ability to re-define how T2DN is treated in the future," he suggests, adding that a positive read out in August should "further solidify XORTX's position as a leading global kidney disease drug developer."

Dr. Davidoff also points out that controlling uric acid levels in diabetes patients may delay progression to end-stage kidney disease, where patients must be on dialysis for four hours a day and only 50% of patients survive two years.

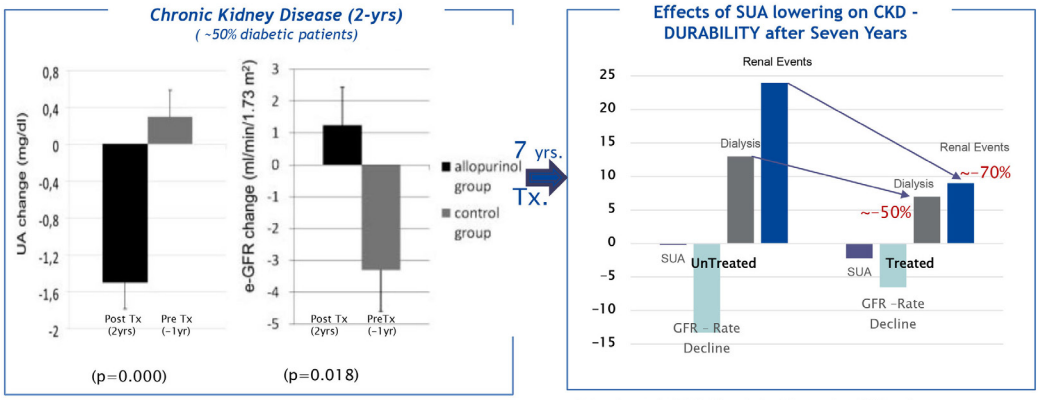
There are no approved diabetic nephropathy drugs to treat progressive kidney disease due to uric acid injury, he notes. "A therapy that maintains and extends kidney health can redefine kidney disease treatment in the future."

Dr. Davidoff says the company's treatment for progressive kidney disease, XRx-221, is a next generation xanthine

oxidoreductase inhibitor, targeting T2DN. “Testing to date suggests that the drug candidate’s high potency inhibits production of uric acid in a large percentage of individuals, decreasing and maintaining serum uric acid levels in low-to-normal target range.”

A study by Spanish researchers published in the peer-reviewed American Journal of Kidney Disease in 2015 showed that after seven years, decreasing serum uric acid in chronic kidney disease patients had the potential to halve the number of individuals who needed dialysis, and cut hospitalizations for renal events by 70%.

Decreasing serum uric acid in T2DN patients has the potential to halve the number of individual who need dialysis!



Goicoechea et al. (2010) Effect of allopurinol in CKD progression and CV risk. Clin J Am Soc Nephrol 5:1388-1393

Goicoechea et al. (2015) Allopurinol and Progression of CKD and Cardiovascular Events: A long-term Follow-up, Am J Kid Dis

Recent Phase 2 Clinical Trial Success in progressive kidney disease increases the probability for translational success of this program

Dr. Davidoff points out that in the U.S., the government covers the $90,000 average annual cost per patient undergoing dialysis. There are now some 10 million people with diabetic nephropathy in the U.S., with forecasts growing to 17 million by 2035. “And with 700,000-to-800,000 people starting dialysis each year, the savings to the health care system would be in the billions of dollars,” he adds.

XORTX hopes to begin a Phase 2b trial with XRx-221 in 400 T2DN patients in 2020, with data expected at the end of 2022. If the study were successful, the company would begin two Phase 3 trials in 2023, releasing data in 2024 and 2025, which could lead to U.S. marketing approval in 2026. The two Phase 3 pivotal studies for the T2DN program are expected to enroll 1,200 patients each.

Along with the Phase 2b study in 2020, the company also plans to conduct a pilot adolescent study with individuals aged 16-to-25. Data should be available by mid-2022. “This group of individuals is particularly at risk of uric acid injury to their kidneys. Recent studies suggest they may respond well to uric acid lowering, so we would expect data to provide some guidance how to proceed to our pivotal studies the following year,” Dr. Davidoff suggests.