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# XORTX Therapeutics – developing First-in-Class Therapies to treat Autosomal Dominant Polycystic Kidney Disease, and drugs for Diabetic Nephropathy and COVID related Chronic Kidney Disease

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**"XORTX's view is that any therapeutic that can intervene in that progression of kidney disease would be highly important and potentially redefine kidney disease treatments and how kidney disease patients are managed in the future." Dr. Allen W. Davidoff, PhD**

**CEOCFO:** ***Dr. Davidoff, you have a great deal of regulatory and upper management experience. What was the reason for founding XORTX Therapeutics? What type of company were you looking to build?***

**Dr. Davidoff:** For our company our senior management team historically had worked on developing a class of drugs in xanthine oxidase inhibitor space and more specifically on developing Oxypurinol. The company was founded originally when we realized there was a series of discoveries and accompanying patents available for the "use of any uric acid lowering agent" to treat a disease axis. Those discoveries focused on the treatment of aberrant purine metabolism and high uric acid, it was realized that these factors modulate progression of disease across a disease axis, which included effects on weight gain so it included obesity, high blood pressure, on the insulin resistance which is recognizable to anyone with prediabetes (metabolic syndrome) or diabetes, and health consequences of diabetes.

We recognized early on that the kidney disease field was largely underserved and because many of these symptoms seemed to be modulated by aberrant purine metabolism and more specifically high uric acid levels. For this reason, an opportunity to introduce a new class of drugs in this field was present. So, that really was the impetus for founding the company and an opportunity to develop and bring a therapy to physicians' hands in service of their patients.

The early steps taken by the company were to aggregate patents related to this disease axis and in this field. Since that time, the Company has continued write new patents that XORTX owns outright. Our overall vision is to fill the unmet medical need with this new class of drugs for diseases such as our lead program XRx-008 for autosomal dominant

polycystic kidney disease, XRx-101 for acute kidney injury due to COVID and of course diabetic neuropathy which represents about half of all individuals with progressive kidney disease.

**CEOCFO:** ***Would you tell us about kidney disease, how it changes patients' lives?***
**Dr. Davidoff:** There are many contributing factors that can affect kidney health and cause harm to kidneys. Diabetes, high blood pressure, weight gain, or diet and exposure to chemicals, infections, genetic factors can initiate or modulate the process. Unfortunately, the influence of many of these factors on kidney health are simply not recognized early enough nor are they treated early until accompanying health issues arise. For physicians when they see a patient, testing high blood pressure or observing vascular issues, cardiovascular issues, or diabetes usually is the first indicator of the presence of kidney disease. In many cases patients with evidence of kidney disease are treated with blood pressure lowering agents or in the case of diabetes, glucose management agents to manage their blood sugar. Unfortunately, there are very few classes of drugs approved, to manage progression of kidney disease. In short, any class of drugs or therapy with the ability to slow or halt progressive kidney disease would greatly affect quality of life and longevity of patients with kidney disease.

How patients experience their kidney disease can vary, for example in autosomal dominant polycystic cystic kidney disease, a physiological transition of an individual's kidneys occurs. The transitioning of a pink fist-sized kidney in their early twenties to a football sized kidney in their mid-fifties. Often that change results in loss of functional kidney tissue accompanied by abdominal pain, progression of markers of their disease, both of which have been described as psychologically challenging. Current therapies for these patients focus on treating high blood pressure, and there is a single drug approved in for ADPKD patients but at present it is only addressing about 5% of individuals, so the ADPKD patient population remains largely underserved.

XORTX believes that we can introduce in the kidney disease field, drugs that address an important mechanism of injury. Once the patient's kidneys fail, the options are dialysis or transplantation and while dialysis is a great tool for keeping uric acid levels low, it is a tool that comes with a substantial social economic burden. Typically, patients on dialysis have to spend hours every other day getting dialysis and that often influences their ability to work. It can be a burden on family and adds strain to the quality of life and quality of social interactions. XORTX's view is that any therapeutic that can intervene in that progression of kidney disease would be highly important and potentially redefine kidney disease treatment and how kidney disease patients are managed in the future.

**CEOCFO:** ***How big a market is it for therapeutics in the kidney arena?***
**Dr. Davidoff:** It is challenging to talk about the dollar values in any kidney disease market but one can generally say that these kidney diseases are underserved. Our focus autosomal dominant polycystic kidney disease has approximately 150 thousand individuals in the US, it is a rare disease and eligible for orphan drug designation and as I

mentioned it is largely unaddressed. There is a single drug approved to slow the growth of cysts in individuals and that drug is addressing about 5% of the market, so 95% of the market is unaddressed.

For diabetic neuropathy, this represents an enormous unaddressed medical need. There are approximately 36 million individuals in the US with diabetes. About 30% to 40% of those will have progressing kidney disease as a result of their diabetes, so that market represents about 12 million. It is notable, that the diabetes and so diabetic kidney disease market is projected to double in size in the next 8 years.

What we are seeing with acute kidney injury due to COVID and the newly emerging chronic kidney injury that is very unique in these individuals, it is difficult to scale but we estimate that the addressable market in the US right now is probably six thousand hospitalized individuals per day. On a yearly basis that is an enormous number. We have done some back-of-the-envelope estimates and there are probably half of the 3.3 million of the hospitalized patients in the last eighteen months would be un-addressable market.

**CEOCFO:** ***XORTX is pioneering new therapies for progressive kidney disease. Why the need for new therapies? What is missing in the current standard of care and drugs?***
**Dr. Davidoff:** The current standard of care involves administration of antihypertensives if you have progressing kidney disease. The kidney plays a fundamental role in management of blood pressure and filtering products of metabolism out of blood for excretion. The ability of the kidney to filter – its filtering capacity – determines whether an individual maintains or accumulates metabolites in their blood. In addition, an individual patient with diabetes might also be prescribed a blood glucose management drug. In diabetic nephropathy for example, antihypertensives are the standard of care, secondarily there are some SGLT2 inhibitors have been recently approved, and also glucose management drugs that are prescribed to patients. We know that diabetes is a complex disease, as is autosomal dominant polycystic kidney disease, and research to define the pathology of these kidney disease and modulating factors in these diseases continues. We remain optimistic that, a sharper definition of the modulators of disease will provide the opportunity to resolve the health problems faced by these patients and slow the progression of their kidney disease.

In undertreated kidney disease fields such as autosomal dominant polycystic kidney disease or diabetic nephropathy, we see the opportunity to intervene, decrease the health consequences associated with aberrant purine metabolism and help patients. Though there is more clinical trial testing that is needed to validate this class of drugs for individuals with progressing kidney disease, a number of successful, independently conducted clinical trials have demonstrated positive results and suggest and opportunity for this class of drug to be helpful. Our understanding of the mechanism of injury in these kidney diseases, and the potential to be the first company to introduce this drug class to autosomal dominant polycystic kidney disease would be gratifying. Similarly, developing this class of drugs to address a large market in diabetic nephropathy and the emerging market in terms of chronic

kidney disease as a result of COVID infection could have an enormous positive impact on patients' lives.

**CEOCFO:** ***Your focus is on managing aberrant purine metabolism and reduce high uric acid and slow progression of kidney disease. How does that help in managing progressive kidney disease?***

**Dr. Davidoff:** Currently published evidence suggests that high uric acid levels are independent risk factors for a number of symptoms that are associated with polycystic kidney disease and polycystic kidney disease progression. Our view of the pathological role of aberrant purine metabolism and high uric acid is that these factors can act as catalyst to accelerate progression of kidney disease.

Published, peer reviewed clinical evidence seems to support the concept that uric acid and aberrant purine metabolism are independent risk factors for increased kidney size, for disease progression at an early age. Published research in a variety of diseases, including kidney disease report that when uric acid is high health consequences related to endothelial dysfunction, declining glomerular function -the units in your kidney that filter blood and excrete uric acid. In ADPKD there is also an increased prevalence of kidney stones. An increasing body of evidence also suggests that uric acid lowering can be beneficial for individuals, and may translate into better outcomes and quality of life for individuals. For these reasons, XORTX is preparing for a Phase 3 clinical trial in ADPKD this year.

The intention of this clinical trial is to establish the safety and benefit of ameliorating aberrant purine metabolism and high uric acid. Therefore, introducing this class of drugs and demonstrate that it can be helpful to these patients, slow their progressing kidney disease and potentially the outcome of their progressive kidney disease is our goal for this year.

**CEOCFO:** ***XORTX has three drug development programs: XRx-008 for Autosomal Dominant Polycystic Kidney Disease (ADPKD), XRx-101 for Coronavirus / COVID-19 infection and XRx-225 for Type 2 Diabetic Nephropathy (T2DN). Would you tell us about them and how far along you are in development with them?***

**Dr. Davidoff:** For our XRx-008 program for autosomal dominant polycystic kidney disease, is our lead program. We are working on delivering a new proprietary formulation of Oxypurinol patients to in that space. We are looking to launch in the second half of 2022 a Phase 3 registration clinical trial to test the benefit of uric acid lowering in individuals with progressing kidney disease due to ADPKD. Similarly, our XRx-101 program is advancing through a bridging pharma kinetics study, thereafter we are planning to initiate a registration clinical trial that is could be completed in as little as seven months. A successful clinical result in that trial could position the company for an emergency-use approval.

Finally, our XRx-225 program is in the early-stage. We are developing new chemical candidates for that space and in that program the next step is animal testing.

**CEOCFO:** ***Would you tell us about the Mt. Sinai study on hospitalized COVID-19 patients? How does COVID affect the kidneys? Is this a study on unvaccinated or vaccinated COVID patients or both?***

**Dr. Davidoff:** We are very pleased with the partnership establishment of Mt. Sinai Hospital in New York. They are one of the leading clinical research groups reporting on COVID in their hospital system. This study which was recently published in the American Journal of Nephrology, looked at patients who were hospitalized between March and December of 2020 and included only patients with confirmed COVID. This study occurred prior to the introduction of vaccines so all patients were unvaccinated. As well the study was restricted to patient who had at least one measure of uric acid during the time that they were hospitalized. The company's interpretation of the study results, are that this study provides evidence and clarifies our view that high serum uric acid may contribute to harm to kidneys, heart and susceptibility to sepsis.

During the last eighteen months or so, accumulating evidence suggested that the virus was first infecting the lungs but then rapidly infecting the vascular system, and the blood vessels of the body. Importantly it was affecting the endothelial lining. There were reports that cell debris from the infection and possibly from a secondary bacterial infection was in circulation, suggesting a need for high purine metabolism to excrete this debris. Interpreted together this evidence hints at a physiological environment that may trigger an increased coagulation and a heightened state of inflammation.

This study showed evidence that in individuals who had been hospitalized, over 50% of them had a unique combination of acute kidney injury and concerningly high uric acid levels. Serum uric acid concentrations of uric acid this high, are at saturating concentrations and imply an environment for formation of uric acid crystals in the circulation. Crystalluria has been associated with acute kidney injury.

Notably, other studies have also shown that acute kidney injury in hospitalized patients with COVID was closely correlated to mortality. The surprising result from that study is that there is a correlation that high uric acid and acute heart injury, and also suggests that the susceptibility to sepsis infection is much higher when uric acid is high in these patients. This study presents compelling and encouraging results for late-stage clinical trials and certainly helps our understanding of how to specifically design and conduct a Phase 3 clinical trial in this patient population.

**CEOCFO:** ***You recently appointed Altasciences as CRO for your clinical study? What did they bring to the table that separates them from other CROs?***

**Dr. Davidoff:** I think when one looks for contract research organizations, there are a number of factors to consider. For XORTX, Altasciences has a well-earned reputation as a quality contract research organization. They have capability, capacity, and the ability to deliver clinical studies in a timely way. For our bridging pharmacokinetics studies which are a couple months in duration, they can complete the test in a timely and competent manner.

**CEOCFO:** ***In November you received approval for listing on the TSX Venture Exchange. What does that mean for XORTX Therapeutics?***
**Dr. Davidoff:** The TSX Venture and of course the Nasdaq listing that we completed this fall, will help graduate XORTX into a broader field of qualified investors and represents an enhanced environment for liquidity. As the company advances our programs, demonstrates clinical and regulatory successes, we anticipate investment interest from a much larger spectrum of investors will be possible. Therefore, this migration of the company to larger US markets represents an important milestone and transition for XORTX.

**CEOCFO:** ***Collaborating with partners seems to be a part of your strategy at XORTX. Why is that? Is it a funding mechanism, for product development, research?***
**Dr. Davidoff:** Strategically whenever there is an opportunity to work with well-established, published, independent researchers, the research is generally of the high quality and the high credibility.

Our job as developers of therapies is to spend our resources and time and staff effectively, and to fundamentally breathe life into projects that merit our best efforts and abandoned those that do not, and that do not stand the test of independent research. From our perspective, development of therapies and independent research that can validate that strength of the science and certainly the strength of the therapeutic concept is a key priority.

Development of therapeutics today is a truly global activity. There are experts across the globe, many can bring results and an independent view to what you are doing and that often results in a highly efficient way to advance your product and bring it to marketing approval as soon as possible.

**CEOCFO:** ***In closing, what should medical professionals, potential partners and investors reading this interview look for from XORTX Therapeutics as we go into a new year? What can we expect for 2022 and why is XORTEX an important company in treating progressive kidney disease?***
**Dr. Davidoff:** We have over the course of the last year successfully raised funding and that funding is translating into a series of research activities over the course of 2021, we are proud to have accomplished a lot as a company this year. 2022 will be an even more exciting year. Our plans include several clinical trials, two of which are late-stage. We have also received numerous inquiries from potential pharma co-development partners regarding our programs, the program status and because of the late-stage progress.

We hope to receive orphan drug status for our XRx-008 program for autosomal dominant polycystic kidney disease, this year, as well. So we are actively working to achieve many of these important milestones in 2022.