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XORTX Announces New Proof of Concept Data in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Independent Study Shows Moderate Dose Strength of XORLO™ Attenuates Kidney Expansion

CALGARY, Alberta, Dec. 08, 2022 (GLOBE NEWSWIRE) -- XORTX Therapeutics Inc. (**"XORTX"** or the "**Company**") (NASDAQ: XRTX | TSXV: XRTX | Frankfurt: ANU), a late stage clinical pharmaceutical company focused on developing innovative therapies to treat progressive kidney disease, is pleased to announce new proof of concept data demonstrating, in a second study, the effectiveness of xanthine oxidase inhibition ("XOI") produced by the Company's proprietary oral oxypurinol formulation, XORLO™, in a mouse model of ADPKD. This study for the XRx-008 program in ADPKD was conducted at the independent laboratory of Dr. Charles Edelstein at the University of Colorado. This new experimental data reproduces the result reported at the American Society of Nephrology meeting held early November 2022 and adds further new evidence that XOI produced by our proprietary formulation of oxypurinol at doses that would be considered moderate-to-low in man is effective at inhibiting the expansion of kidneys in ADPKD.

This study was designed to investigate several key aspects of polycystic kidney disease ("PKD"):

1. If Xanthine oxidase (XO) is expressed in the mouse RC/RC model of polycystic kidney disease ("PKD"), a model for human ADPKD.

2. How increased circulating uric acid concentrations in the cardiovascular system affect kidney weight, heart, inflammatory status and fibrosis.

3. How inhibiting of XO by XORTX's proprietary XRx-008 formulation of oxypurinol, XORLO™, attenuates total kidney volume, cyst genesis and cyst growth rate.

While analysis of evidence is ongoing, the key results of this study show that:

1/ Aberrant purine metabolism is substantially and significantly increased - as indicated by an increased kidney tissue expression of XO and increased activity of the enzyme in ADPKD tissue is present;

2/ When circulating serum uric acid is increased in mouse ADPKD models there is an accompanying increase of kidney volume and decreased filtering capacity; and

3/ The XRx-008 formulation of oxypurinol, XORLO™, attenuates the mechanism of injury

associated with chronically increased uric acid.

Dr. Allen Davidoff, CEO of XORTX stated, “The new results from this independently conducted study shows that XORTX’s proprietary formulation, at dose similar to what would be anticipated in XORTX’s upcoming phase 3 clinical trial, is sufficient to suppress the harmful effects of chronically high uric acid in ADPKD. We believe this result further confirms and guides our conduct of future human clinical trials.”

About Hyperuricemia and Total Kidney Volume (TKV) in human ADPKD

In individuals with ADPKD, expansion of kidney size is considered an important measure of disease diagnosis and progression. The continuous growth of kidney cysts leads to an exponential growth in total kidney volume (“TKV”) accompanied by tissue damage and fibrosis and eventual decline in function, resulting in kidney failure. Several clinical studies report[1] that high chronic serum uric acid (Hyperuricemia) is frequently present in mid to late stage ADPKD Riviera[2], Mejias[3], Helal[4] and Han[5], with some of these studies correlating serum uric acid concentration with increased total kidney volume. Helal et al, concludes that after adjusting for age, gender and creatinine clearance, there was a 5.8% increase in TKV for every 1 mg/dL increase in uric acid($p<0.01$)[4]. Negotiations with the US Food and Drug Administration (“FDA”), European Medicines Agency and Health Canada have set a precedent for using a reasonably likely surrogate efficacy biomarker (TKV) toward accelerated approval after an interim analysis, with full approval contingent on the success of an accepted clinical end point (*e.g.*, 30% decline in eGFR by the conclusion of the trial)[7].

In recent years, the FDA has qualified total kidney volume as an approvable endpoint and therapeutics that demonstrate the ability to slow the expansion of kidney volume may be eligible for accelerated marketing approval[5].

About the Mouse RC/RC Model of Polycystic Kidney Disease

Furthermore in 2012, Katharina Hopp et al. described a new genetic murine model - the *Pkd1RC/RC* mouse[8,9]. *Pkd1RC/RC* mouse develops a slowly progressing polycystic kidney disease with embryonic cyst initiation, present cystic lesions in the liver and elongated primary cilia in collecting ducts. The slowly progressive nature of the disease in this model, as well as the clinical relevance of the introduced mutation make it particularly interesting for the study of ADPKD. Its validity as a preclinical model for ADPKD drug efficiency studies was further established by the observation of a positive effect of tolvaptan in this model.

References:

1. Hoover E, et al., Design and Basic Characteristics of a National Patient-Powered Registry in ADPKD, Kidney 360, Vol 3, 1350-1358, 2022
2. Rivera et al, Association of Hyperuricemia and Polycystic Kidney Disease, Bol Assoc Med P. Rico, Mayo, 1965
3. Mejias et al, Hyperuricemia, Gout and Autosomal Dominant Polycystic Kidney Disease, Am J Med Sci, Vol 297, No 3, 145, 1989
4. Helal I., et al, and Fick-Bronanhan GM., Serum Uric Acid, Kidney Volume, and Progression in Autosomal-dominant Polycystic Kidney Disease, Nephrol Dial

Transplant, Vol 28, 380-385, 2013
5. Han M., Hyperuricemia and deterioration of renal function in Autosomal Dominant Polycystic Kidney Disease, BMC Nephrology, Vol 15, 63, 2014
6. FDA Qualification of TKV: https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/reviews-qualification-biomarker-total-kidney-volume-studies-treatment-autosomal-dominant-polycystic
7. Smith KA, et al., and Perrone RD, Addressing the need for clinical trial end points in autosomal dominant polycystic kidney disease: A report from the Polycystic Kidney Disease Outcomes Consortium (PKDOC). Am J Kidney Dis 73: 533–541, 2019
8. Koslowski S, et al., An Overview of In Vivo and InVitro Models for ADPKD, Int J Mol Sci, Vol 21, 4537, 2022
9. Hopp K., et al, Functional Polycystin-1 dosage governs autosomal dominant polycystic kidney disease severity, J Clin Investig, 122, 4257, 2012

About XORTX Therapeutics Inc.

XORTX is a pharmaceutical company with two clinically advanced products in development: 1) our lead, XRx-008 program for ADPKD; and 2) our secondary program in XRx-101 for acute kidney and other acute organ injury associated with Coronavirus / COVID-19 infection. In addition, XRx-225 is a pre-clinical stage program for Type 2 Diabetic Nephropathy. XORTX is working to advance its clinical development stage products that target aberrant purine metabolism and xanthine oxidase to decrease or inhibit production of uric acid. At XORTX, we are dedicated to developing medications to improve the quality of life and future health of patients. Additional information on XORTX is available at www.xortx.com.

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This press release contains express or implied forward-looking statements pursuant to U.S. Federal securities laws. These forward-looking statements and their implications are based on the current expectations of the management of XORTX only, and are subject to a number of factors and uncertainties that could cause actual results to differ materially from those described in the forward-looking statements. Except as otherwise required by law, XORTX undertakes no obligation to publicly release any revisions to these forward-looking statements to reflect events or circumstances after the date hereof or to reflect the

occurrence of unanticipated events. More detailed information about the risks and uncertainties affecting XORTX is contained under the heading “Risk Factors” in XORTX’s Registration Statement on Form F-1 filed with the SEC, which is available on the SEC's website, www.sec.gov (including any documents forming a part thereof or incorporated by reference therein), as well as in our reports, public disclosure documents and other filings with the securities commissions and other regulatory bodies in Canada, which are available on www.sedar.com.

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