Vertex Provides Updates on Multiple Kidney Programs at the American Society of Nephrology (ASN) Annual Kidney Week Congress

October 25, 2024

- New data on povetacicept 80 mg SC Q4 weeks in IgA nephropathy shows mean UPCR reduction from baseline of 66% observed at 48 weeks, associated with stable renal function (eGFR) and 63% achieving clinical remission --

- First proteinuria data on povetacicept in primary membranous nephropathy shows mean UPCR reduction from baseline of 62% at 24 weeks –

- Global Phase 3 RAINIER trial of povetacicept in IgA nephropathy now underway –

– Enrollment and dosing ongoing in Phase 3 portion of the global Phase 2/3 pivotal clinical trial of inaxaplin for the treatment of APOL1-mediated kidney disease –

BOSTON--(BUSINESS WIRE)--Oct. 25, 2024-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today provided updates on multiple kidney diseases in its pipeline including IgA nephropathy (IgAN), primary membranous nephropathy (pMN), and APOL1-mediated kidney disease (AMKD). These updates demonstrate the transformative potential of Vertex's investigational therapies in multiple serious kidney diseases, and include positive new data on povetacicept, a dual inhibitor of the BAFF and APRIL pathways, in IgAN and pMN, presented at the American Society of Nephrology's (ASN) Kidney Week Congress on October 23-27 in San Diego, California.

"We are very pleased with the broadening of our innovative pipeline in renal medicine which now spans programs in AMKD, IgAN, pMN and polycystic kidney disease," said Carmen Bozic, M.D., Executive Vice President, Global Medicines Development and Medical Affairs, and Chief Medical Officer at Vertex. "The new data in IgAN and pMN we shared at this year's ASN congress continue to reinforce povetacicept as a potential best-in-class therapy and demonstrate its potential as a pipeline-in-a-product. We also continue to make progress in AMKD and autosomal dominant polycystic kidney disease (ADPKD) where we are advancing the first potential treatments to address the underlying cause of these diseases."

Povetacicept in IgAN

Vertex presented data on 54 patients with IgAN who received povetacicept 80 mg or 240 mg subcutaneously every 4 weeks (SC Q4W). Treatment with povetacicept 80 mg SC Q4W demonstrated a clinically meaningful decrease in proteinuria, with a mean 66% reduction from baseline in urine protein to creatinine ratio at 48 weeks (UPCR; n=8) associated with stable renal function over 48 weeks as assessed by estimated glomerular filtration rate (eGFR). By 48 weeks, 63% (5 out of 8) of study participants achieved clinical remission, defined as UPCR <0.5 g/g, negative hematuria and stable renal function (<25% reduction in eGFR from baseline).

Treatment with povetacicept 240 mg SC Q4W was associated with similar improvements in proteinuria along with stable renal function.

Both doses have been well tolerated in patients with IgAN. The majority of adverse events (AEs) were mild or moderate in severity, and there were no serious adverse events (SAEs) related to povetacicept.

Vertex has now initiated RAINIER, a global Phase 3 clinical trial of povetacicept 80 mg in IgAN.

A poster presentation #FR-PO854 entitled "Results from Longer Follow-Up with Povetacicept, an Enhanced Dual BAFF/APRIL Antagonist, in IgA Nephropathy (RUBY-3 Study)" was presented during the poster session on October 25 from 10:00 a.m. to 12:00 p.m. PDT.

Povetacicept in pMN

Vertex also presented emerging data in patients with pMN who received povetacicept 80 mg SC Q4W, with three patients having completed at least 24 weeks of treatment. Treatment with povetacicept demonstrated a mean 62% reduction from baseline in UPCR at 24 weeks, associated with stable renal function. By week 24, 67% (2 out of 3) study participants had achieved partial clinical remission, defined as UPCR <3.5 g/g and >50% reduction in UPCR from baseline. Anti-PLA2R1 autoantibodies, which are a marker of disease activity and associated with clinical outcomes, decreased from baseline by a mean of 87% at week 20.

Povetacicept was well tolerated in patients with pMN, with AEs that were mild or moderate in severity. There were no SAEs related to povetacicept.

A poster presentation #TH-PO589 entitled "Updated Results with Povetacicept, an Enhanced Dual BAFF/APRIL Antagonist, in Primary Membranous Nephropathy (RUBY-3 Study)" was presented during the poster session on October 24 from 10:00 a.m. to 12:00 p.m. PDT.

AMKD

Vertex is developing inaxaplin, a potential first-in-class, investigational, oral small molecule inhibitor of APOL1, with the goal of targeting the underlying cause of AMKD. Enrollment and dosing are ongoing in the Phase 3 portion of the global Phase 2/3 pivotal AMPLITUDE clinical trial of inaxaplin.

Vertex has the following AMKD poster presentations at ASN:

- Poster presentation #TH-P01203 entitled "AMPLITUDE: A Phase 2/3 Adaptive Trial of Inaxaplin in APOL1-mediated Kidney Disease" was presented during the poster session on October 24 from 10:00 a.m. to 12:00 p.m. PDT.
- Poster presentation #SA-PO701 entitled "Small Molecule *APOL1* Channel Inhibitor Reduces Proteinuria, Rescues

Podocyte Injury, and Reverses eGFR Decline in an APOL1-Mediated Kidney Disease Mouse Model" will be presented during the poster session on October 26 from 10:00 a.m. to 12:00 p.m. PDT.

- Poster presentation #SA-PO700 entitled "Small Molecule Inhibition of *APOL1* Channel Activity Protects Podocytes from Mitochondrial Dysfunction, Cell Death and Barrier Disruption Induced by *APOL1* Risk Variants" will be presented during the poster session on October 26 from 10:00 a.m. to 12:00 p.m. PDT.

All accepted abstracts are available online on the ASN website.

About IgA Nephropathy (IgAN)

IgAN is a serious, progressive, life-threatening, B cell-mediated chronic kidney disease that is the most common cause of primary (idiopathic) glomerulonephritis, affecting people worldwide including approximately 130,000 people in the U.S. IgAN results from deposition of circulating immune complexes consisting of immunoglobulins and galactose-deficient immunoglobulin A (Gd-IgA1) in the renal glomerular mesangium, triggering kidney injury and fibrosis. A high percentage of people with IgAN progress to end-stage renal disease. There are no approved therapies that specifically target the underlying cause of IgAN.

About RAINIER

RAINIER is a global Phase 3 pivotal trial of povetacicept 80 mg vs. placebo on top of standard of care in approximately 480 people with IgAN. The study is designed to have a pre-planned interim analysis evaluating UPCR for the povetacicept arm versus placebo after a certain number of patients reach 36 weeks of treatment. If positive, the interim analysis may serve as the basis for Vertex to seek accelerated approval in the U.S. Final analysis will occur at two years of treatment, with a primary endpoint of total eGFR slope through Week 104.

About Primary Membranous Nephropathy (pMN)

Primary membranous nephropathy is a serious, progressive, life-threatening B cell-mediated chronic kidney disease affecting people worldwide, with approximately 60,000 people diagnosed in the U.S. pMN causes a patient's immune system to damage the glomeruli and may cause progressive loss of kidney function. There are no approved therapies that specifically target the underlying cause of pMN.

About RUBY-3

RUBY-3 is an ongoing, multiple ascending dose, multi-cohort, open label, Phase 1/2 basket study of povetacicept in autoimmune glomerulonephritis, including IgAN, pMN, lupus nephritis and ANCA-associated vasculitis with glomerulonephritis where povetacicept is being administered subcutaneously for up to 104 weeks.

About Povetacicept

Povetacicept is a dual antagonist of the BAFF (B cell activating factor) and APRIL (a proliferation inducing ligand) cytokines, which play key roles in pathogenesis of multiple autoimmune diseases via their roles in the activation, differentiation and/or survival of B cells, T cells and innate immune cells. Based upon an engineered TACI (transmembrane activator and CAML interactor) domain, povetacicept has higher binding affinity and greater potency in preclinical studies versus other inhibitors of BAFF and/or APRIL alone and has demonstrated potential best-in-class efficacy in a clinical trial in patients with IgA nephropathy and primary membranous nephropathy. Povetacicept is also in development for multiple serious diseases including other autoimmune kidney diseases and autoimmune cytopenias.

About APOL1-Mediated Kidney Disease (AMKD)

AMKD is a genetic kidney disease affecting approximately 100,000 people in the U.S. and Europe. AMKD is caused by two variants of the *APOL1* gene, which exert a toxic effect on kidney cells, leading to cell injury, cell death and damage to glomeruli (which filter blood to the kidney). Even after treatment with currently available therapies, people with AMKD often progress to kidney failure. Kidney failure is treated with frequent, long-term dialysis or a kidney transplant. Both require lifelong treatment and follow-up and carry a high mortality risk**.** There are currently no approved treatments that address the underlying cause of AMKD.

About Inaxaplin

Inaxaplin is a potential first-in-class, investigational small molecule inhibitor of APOL1, and the first investigational therapy aimed at treating the underlying cause of AMKD.

About AMPLITUDE

AMPLITUDE is a global Phase 2/3 pivotal trial of inaxaplin for the treatment of AMKD, in which a 45 mg once daily oral dose is compared to placebo, on top of standard of care. The study is designed to have a pre-planned interim analysis at Week 48 evaluating estimated glomerular filtration rate (eGFR) slope, a measure of kidney function, supported by a percent change from baseline in proteinuria, in the inaxaplin arm versus placebo. If positive, the interim analysis may serve as the basis for Vertex to seek accelerated approval in the U.S. Enrollment and dosing are ongoing in the Phase 3 portion of the study.

About Autosomal Dominant Polycystic Kidney Disease (ADPKD)

ADPKD is the most common inherited kidney disease and one of the most common severe Mendelian genetic diseases, affecting approximately 250,000 diagnosed people in the U.S. and Europe. As an autosomal dominant disease, one affected parent can pass on the disease to their children.

In most cases, ADPKD is caused by variants in the *PKD1* and *PKD2* genes, which express proteins known as polycystins. The majority of ADPKD patients (~80%) have a variant in the *PKD1* gene, resulting in a loss of function of polycystin 1 (PC1). This leads to the proliferation of kidney epithelial cells, increased fluid secretion and the formation and expansion of numerous fluid-filled cysts. The progressive cyst formation causes an increase in kidney size and decline in kidney function. Around half of patients with ADPKD experience kidney failure by the age of 60. Kidney cysts can also lead to severe abdominal pain, cyst infection, blood in the urine and kidney stones, all of which significantly impair quality of life.

About Vertex

Vertex is a global biotechnology company that invests in scientific innovation to create transformative medicines for people with serious diseases. The company has approved medicines that treat the underlying causes of multiple chronic, life-shortening genetic diseases — cystic fibrosis, sickle cell disease and transfusion-dependent beta thalassemia — and continues to advance clinical and research programs in these diseases.Vertex also has a robust clinical pipeline of investigational therapies across a range of modalities in other serious diseases where it has deep insight into causal human biology, including acute and neuropathic pain, APOL1-mediated kidney disease, IgA nephropathy, primary membranous nephropathy, autosomal dominant polycystic kidney disease, type 1 diabetes and myotonic dystrophy type 1.

Vertex was founded in 1989 and has its global headquarters in Boston, with international headquarters in London. Additionally, the company has research and development sites and commercial offices in North America, Europe, Australia, Latin America and the Middle East. Vertex is consistently recognized as one of the industry's top places to work, including 15 consecutive years on Science magazine's Top Employers list and one of Fortune's 100 Best Companies to Work For. For company updates and to learn more about Vertex's history of innovation, visit www.vrtx.com or follow us on LinkedIn, Facebook, Instagram, YouTube and X.

Vertex Special Note Regarding Forward-Looking Statements

This press release contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, the statements by Carmen Bozic, M.D., in this press release, and statements regarding Vertex's expectations and plans for the global Phase 3 RAINIER study of povetacicept, including the potential for an interim analysis to serve as the basis to seek accelerated approval in the U.S., and expectations and plans for the Phase 3 portion of the clinical trial of inaxaplin, including the potential for an interim analysis to serve as the basis to seek accelerated approval in the U.S. While we believe the forward-looking statements contained in this press release are accurate, these forward-looking statements represent the company's beliefs only as of the date of this press release and there are a number of risks and uncertainties that could cause actual events or results to differ materially from those expressed or implied by such forward-looking statements. Those risks and uncertainties include, among other things, that data from the company's development programs may not support registration or further development of its compounds due to safety, efficacy, and other reasons, and other risks listed under the heading "Risk Factors" in Vertex's most recent annual report and subsequent quarterly reports filed with the Securities and Exchange Commission at www.sec.gov and available through the company's website at www.vrtx.com. You should not place undue reliance on these statements, or the scientific data presented. Vertex disclaims any obligation to update the information contained in this press release as new information becomes available.

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