Vertex Announces Positive Week 36 Interim Analysis Results for Primary and All Secondary Endpoints in the RAINIER Phase 3 Trial of Povetacicept in Adults With IgA Nephropathy

- *For the primary endpoint, patients treated with povetacicept achieved a 52.0% reduction from baseline in proteinuria as measured by 24-hour urine protein to creatinine ratio (UPCR) and achieved a statistically significant and clinically meaningful 49.8% reduction in UPCR versus placebo (P<0.0001) –*

- *For the first secondary endpoint, povetacicept treatment led to a 77.4% reduction from baseline in serum Gd-IgA1, resulting in a statistically significant and clinically meaningful reduction of 79.3% (P<0.0001) versus placebo; for the second secondary endpoint, 85.1% of povetacicept-treated patients achieved hematuria resolution, resulting in a statistically significant and clinically meaningful improvement of 61.7% (P<0.0001) versus placebo –*

- *Povetacicept was generally safe and well tolerated –*

- *Vertex to complete Biologics License Application by the end of March for potential U.S. Accelerated Approval –*

BOSTON – March 9, 2026 – Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced positive data from a pre-specified Week 36 interim analysis of the ongoing Phase 3 RAINIER trial of povetacicept, an engineered fusion protein and dual inhibitor of the BAFF (B cell activating factor) and APRIL (a proliferation inducing ligand) cytokines, in immunoglobulin A nephropathy (IgAN).

The trial met its primary objective. In the interim analysis population, patients treated with povetacicept achieved a 52.0% reduction from baseline in urine protein to creatinine ratio (UPCR) at Week 36, with a statistically significant and clinically meaningful 49.8% UPCR reduction compared to placebo (*P*<0.0001). The reduction in proteinuria was consistent across all pre-specified subgroups.

The trial also met its secondary objective. For the first secondary endpoint, patients treated with povetacicept demonstrated a 77.4% reduction from baseline in serum galactose deficient IgA1 (Gd-IgA1) compared to an increase of +9.1% in the placebo group, yielding a reduction of 79.3% compared to placebo (*P*<0.0001). For the second secondary endpoint, in patients with baseline hematuria, 85.1% achieved hematuria resolution in the povetacicept treatment group compared to 23.4% in the placebo group, resulting in hematuria resolution of 61.7% compared to placebo (*P*<0.0001).

Povetacicept was generally safe and well tolerated. The majority of adverse events (AEs) were mild to moderate. There were no serious adverse events (SAEs) related to povetacicept and no deaths in the trial. There were no opportunistic infections, and no discontinuations due to infections. As expected, anti-drug antibodies (ADAs) were observed; these ADAs had no impact on efficacy or the risk profile.

Treatment discontinuations (for any reason) were 8.8% in the placebo group and 3.8% in the povetacicept group, and trial discontinuations (for any reason) were 1.5% in the placebo group and 0.8% in the povetacicept group in this interim analysis population.

“The Phase 3 RAINIER 36-week interim analysis results in IgAN are remarkable. With its clinical profile, dosing and administration advantage, and breadth of potential indications, povetacicept demonstrates best-in-class potential and establishes renal medicine as Vertex’s fourth franchise alongside cystic

fibrosis, hematology and acute pain," said Reshma Kewalramani, M.D., FASN, Chief Executive Officer and President of Vertex. "As a nephrologist, I am struck by the rapid, deep and sustained response to povetacicept, as well as the consistency of benefit across all subgroups. These results are important for patients with IgAN and also bring us one step closer to realizing povetacicept's pipeline-in-a-product promise. We thank the patients and trial investigators for their trust and for making RAINIER the largest and fastest enrolling of any contemporary IgAN trial."

Trial Design, Population Characteristics and Efficacy Results

RAINIER is a global Phase 3 randomized, double-blind, placebo-controlled pivotal trial of povetacicept 80 mg administered subcutaneously every four weeks versus placebo on top of standard of care.

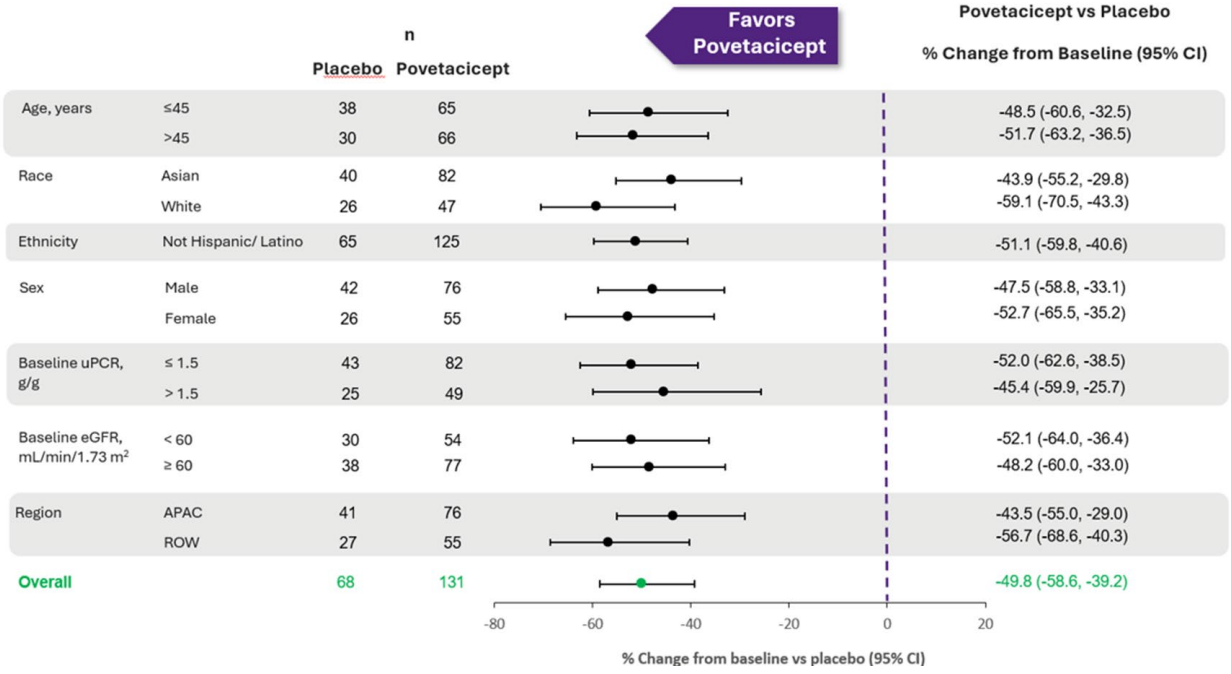
A total of 605 patients were randomized in the trial, N=557 are in the main cohort, of which N=199 are in the interim analysis population, and N=48 patients are in an exploratory cohort. These patients are representative of real world IgAN patients at risk of kidney disease progression. The median time from diagnosis of IgAN to randomization in the main cohort was approximately 3.8 years and the trial patients had high rates of background supportive care, with 97.8% of patients on angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEi/ARBs), and 67.7% of patients on sodium-glucose co-transporter 2 (SGLT2) inhibitors, the latter representing the highest percentage in recently completed IgAN trials.

For the interim analysis, the trial's primary endpoint is percent change from baseline in 24-hour UPCR, and the two alpha-controlled secondary endpoints are percent change from baseline in serum Gd-IgA1 and the proportion of patients to achieve hematuria resolution, all at Week 36. Exploratory endpoints for this interim analysis included the proportion of patients with 24-hour UPCR <0.5 g/g, in line with the most recent Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.

Efficacy Results for the RAINIER Interim Analysis Population at Week 36		
	Placebo N=68	**Povetacicept N=131**
Primary Endpoint		
% change from baseline in 24-hr UPCR	-4.3	-52.0
% change versus placebo		**-49.8**
P value vs. placebo[a]		<0.0001
Secondary Endpoint: Gd-IgA1		
% change from baseline in serum Gd-IgA1	+9.1	-77.4
% change versus placebo		**-79.3**
P value vs. placebo[a]		<0.0001
Secondary Endpoint: Hematuria Resolution[b]		
proportion of patients achieving resolution (%)	23.4	85.1
difference in proportion versus placebo (%)		**61.7**
P value vs. placebo[a]		<0.0001
Select Exploratory Endpoint		
proportion of patients achieving 24-hour UPCR <0.5 g/g (%)	6.2	42.2

[a]Two-sided *P* value.
[b]Hematuria resolution in patients who had hematuria at baseline (N=36 for placebo and N=67 for povetacicept groups).

Figure 1: Pre-specified Subgroup Analysis in Percent Change from Baseline in 24-Hour UPCR at Week 36



Safety Results

Povetacicept was generally safe and well tolerated. The data below reflect 557 patients in the main cohort with a mean duration of treatment of 33.7 weeks for the povetacicept cohort and 33.4 weeks for placebo.

Adverse Events Occurring During the Treatment Period in the Safety Population		
	Placebo N=185 n (%)	**Povetacicept N=372 n (%)**
Patients with any adverse event during the treatment emergent period	145 (78.4)	279 (75.0)
Adverse events occurring in ≥10% of patients in either group		
Upper respiratory tract infection	21 (11.4)	68 (18.3)
Nasopharyngitis	23 (12.4)	36 (9.7)
Injection site reactions[a]	4 (2.2)	54 (14.5)

[a]Injection site reactions (ISR) were identified using a pre-specified set of Preferred Terms (including, for example, injection site reaction and injection site erythema). All ISRs were non-serious and mild or moderate in severity.

Serious AEs occurred in 4.3% (8 out of 185 patients) of the placebo group and 3.0% (11 out of 372 patients) of the povetacicept group. The same incidence of SAEs of infection (0.5%) occurred in both the placebo and povetacicept groups.

Next Steps

The U.S. Food and Drug Administration (FDA) has granted rolling review of the Biologics License Application (BLA) for povetacicept in IgAN. As such, Vertex has already submitted several modules and will complete the full BLA submission by the end of March for potential accelerated approval. As announced previously, Vertex is using a priority review voucher to expedite the review of the povetacicept BLA from ten months to six months.

If povetacicept is approved by the FDA, Vertex plans to launch povetacicept in a low volume (<0.5 mL) subcutaneous auto-injector delivered once every four weeks via at-home administration.

The RAINIER Phase 3 trial continues in a blinded manner, and final analysis will occur at two years of treatment, with a primary endpoint of total estimated glomerular filtration rate (eGFR) slope through Week 104. Full enrollment for the RAINIER trial was announced in November 2025.

About Povetacicept
Povetacicept is a dual inhibitor of the BAFF and APRIL cytokines, which promote B cell activation, differentiation and/or survival, and provides B cell control by inhibiting the ability of BAFF and APRIL to drive the pathogenesis of multiple autoimmune diseases. Due to its engineered TACI domain, povetacicept has demonstrated improved binding affinity, potency, pharmacokinetics, and/or tissue distribution compared to other APRIL, BAFF, and dual BAFF+APRIL inhibitors in preclinical studies.

Povetacicept has received FDA Breakthrough Therapy Designation for the treatment of IgAN. As announced late last year, FDA also granted rolling review of the BLA for povetacicept in IgAN.

Povetacicept is the only dual BAFF+APRIL inhibitor in pivotal trials for multiple kidney diseases. Expansion into additional indications for povetacicept is advancing with the ongoing Phase 2/3 OLYMPUS trial in primary membranous nephropathy (pMN) and the expected start of the ETNA Phase 2 trial in generalized myasthenia gravis (gMG) in the first half of 2026.

Povetacicept is an investigational agent and has not been approved by health authorities.

About IgA Nephropathy (IgAN)
IgAN is a serious, progressive, life-threatening kidney disease driven by uncontrolled autoreactive B cell activity and is the most common cause of primary glomerulonephritis, affecting approximately 330,000 people in the United States and Europe and more than 1.5 million globally. IgAN results from the 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. Up to 72% of adult IgAN patients progress to end-stage renal disease or death within 20 years of diagnosis.

About RAINIER

RAINIER (NCT06564142) is a global Phase 3 randomized, double-blind, placebo-controlled pivotal trial of povetacicept 80 mg administered subcutaneously every four weeks vs. placebo on top of standard of care in adults with IgAN. A total of 605 patients were randomized in the trial, of which N=557 were randomized in the main cohort and N=48 in an exploratory cohort. The inclusion criteria were the same for both cohorts, except that the eGFR for the main cohort was ≥30 mL/min/1.73m^2, and for the exploratory cohort it was 20 to <30 mL/min/1.73m^2.

The trial was designed to have a pre-planned interim analysis when a pre-specified number of patients complete 36 weeks of treatment. The interim analysis population for efficacy was N=199 and is a subset of the main cohort. The trial's primary endpoint at the interim analysis is percent change from baseline in 24-hour UPCR at Week 36, and two alpha-controlled secondary endpoints are percent change from baseline in serum Gd-IgA1 and the proportion of patients to achieve hematuria resolution (among patients with hematuria at baseline) also at Week 36. The main cohort, N=557, serves as the primary population for the assessment of safety. Final analysis will occur at two years of treatment, with a primary endpoint of total estimated glomerular filtration rate (eGFR) slope through Week 104.

RAINIER is the largest trial conducted in IgAN and achieved full enrollment faster than any contemporary IgAN trial.

About Vertex
Vertex is a global biotechnology company that invests in scientific innovation to create transformative medicines for people with serious diseases and conditions. The company has approved therapies for cystic fibrosis, sickle cell disease, transfusion-dependent beta thalassemia and acute pain, and it continues to advance clinical and research programs in these areas. 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 IgA nephropathy, neuropathic pain, APOL1-mediated kidney disease, primary membranous nephropathy, autosomal dominant polycystic kidney disease, type 1 diabetes, generalized myasthenia gravis, 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 16 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.

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 made by Reshma Kewalramani, M.D., FASN, statements about the timing of the company's completion of the full BLA submission for povetacicept in IgAN for potential accelerated approval in the U.S., expectations for povetacicept's best-in-class potential and pipeline-in-a-product potential, Vertex's plans regarding the potential launch of povetacicept, the status of the RAINIER Phase 3 trial and expectations regarding the final analysis from this trial, the clinical status of and expectations for the OLYMPUS Phase 2/3 trial in pMN and the expected start of the ETNA Phase 2 trial in gMG. While Vertex believes 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 the company may be unable to make the anticipated regulatory submissions on the expected timeline, or at all, that data from the company's research and development programs may not support registration or further development of its compounds due to safety, efficacy, and other risks, 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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