

Kidney Program Updates at the American Society of Nephrology Kidney Week 2026

October 23, 2026

Presentation intended for the investment community

©2026 Vertex Pharmaceuticals Incorporated

Agenda

Welcome

Susie Lisa, CFA, Senior Vice President, Investor Relations, Vertex Pharmaceuticals

Kidney portfolio overview

Reshma Kewalramani, M.D., President and Chief Executive Officer, Vertex Pharmaceuticals

Inaxaplin in AMKD

Akinlolu Ojo, M.D., Ph.D., MBA; Executive Dean of the School of Medicine at the University of Kansas; Professor, Nephrology and Hypertension; Professor, Population Health

Povetacicept in IgAN

Richard Lafayette, M.D., Professor of Medicine (Nephrology) at the Stanford University Medical Center; Founder and Director of the Stanford Glomerular Disease Center

Q&A Session

Dr. Kewalramani, Dr. Ojo, Dr. Lafayette

Safe harbor statement

This presentation contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, statements regarding Vertex's expectations for its renal programs, including expectations that the company's four renal programs have first-in-class and/or best-in-class potential, beliefs regarding the commercial potential for the company's renal programs, beliefs regarding the expected patient populations for the company's renal programs, expectations to have four potential kidney launches by 2030, anticipated clinical benefits of inaxaplin, povetacicept and VX-407, expectations regarding the November 30 PDUFA date for povetacicept in IgAN, and expectations for the availability of interim analysis data in the AMKD AMPLITUDE study in early 2027. While Vertex believes the forward-looking statements contained in this presentation are accurate, these forward-looking statements represent the company's beliefs only as of the date of this presentation 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 pipeline programs may not be available and/or support registration or further development of its potential medicines due to safety, efficacy or other reasons, that the company may be unable to successfully commercialize its renal programs, and other risks listed under “Risk Factors” in Vertex's annual report filed with the Securities and Exchange Commission (SEC) and available through the company's website at www.vrtx.com and on the SEC’s website at www.sec.gov. 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 presentation as new information becomes available.

©2026 Vertex Pharmaceuticals Incorporated

Vertex's differentiated, disease-first R&D strategy has delivered four renal programs

Each with first-in-class and/or best-in-class potential

R+D strategy centered on:

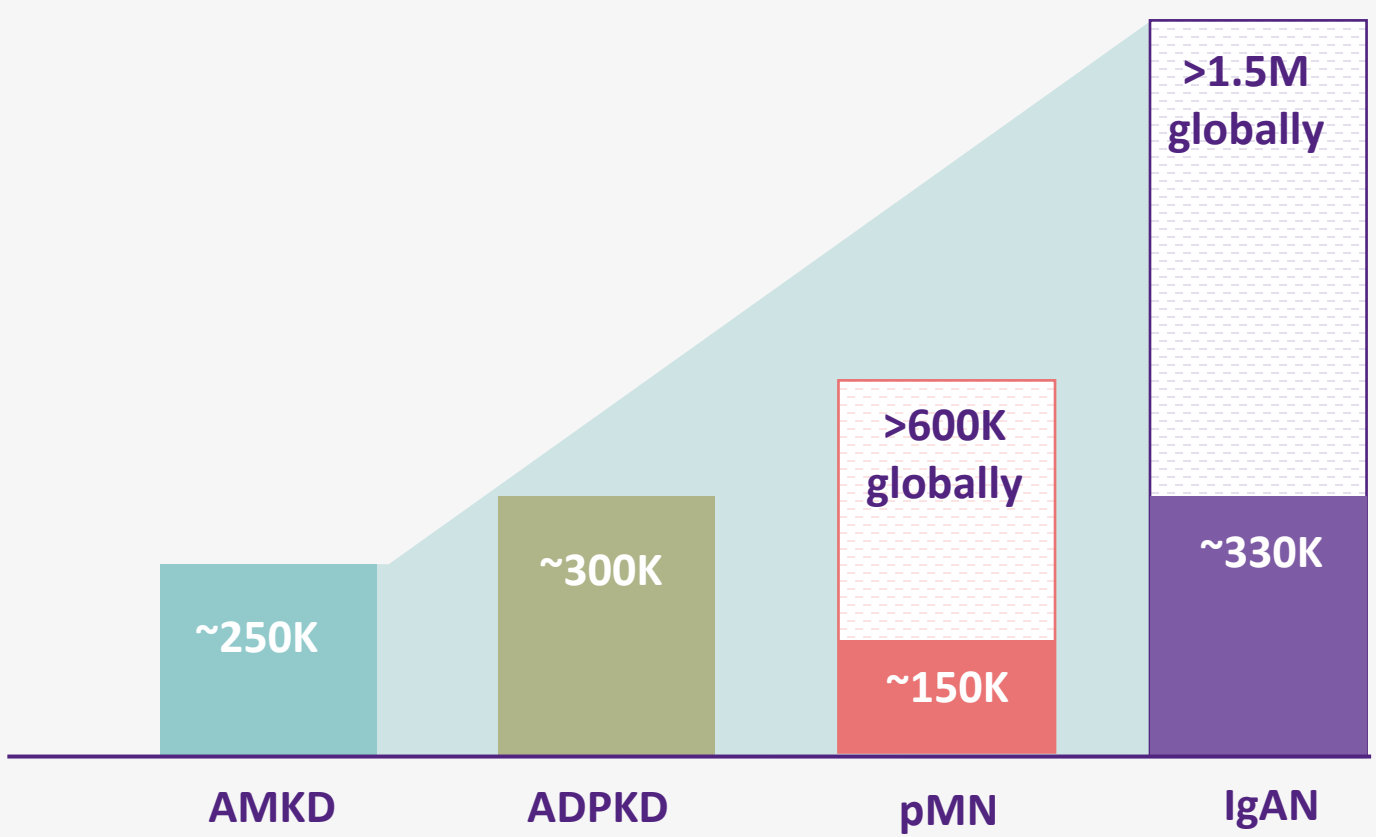
- High unmet need
- Causal human biology is known
- Validated targets
- Biomarkers that translate from bench to bedside
- Efficient development and regulatory pathways

- **APOL1-Mediated Kidney Disease (AMKD)**
- **Immunoglobulin-A nephropathy (IgAN)**
- **Primary membranous nephropathy (pMN)**
- **Autosomal Dominant Polycystic Kidney Disease (ADPKD)**

©2026 Vertex Pharmaceuticals Incorporated

High unmet need + large patient populations = significant opportunity in renal diseases

Vertex seeks to lead the renaissance in renal medicine



ULTIMATE ADDRESSABLE PATIENT POPULATION*

3
programs in pivotal development

4
potential kidney launches by 2030

>$13B
over time, renal programs could rival CF in terms of revenue

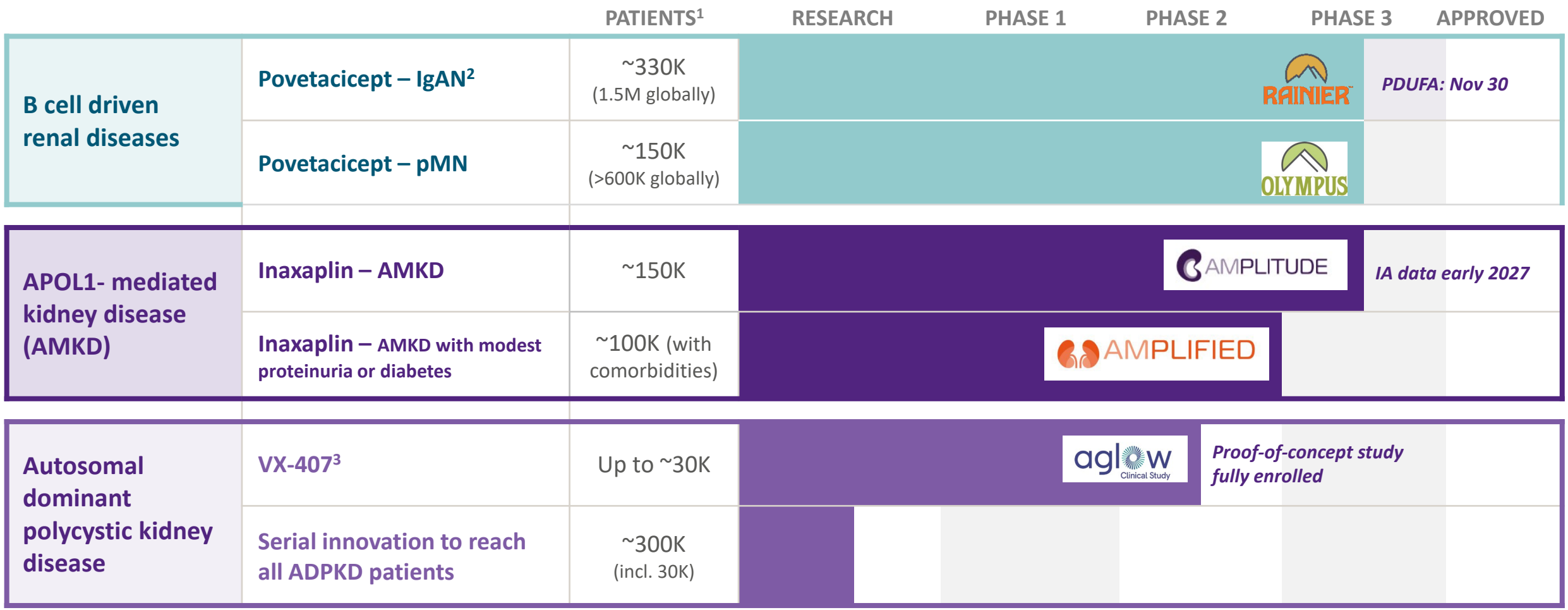
*Epidemiological estimates include patients in the U.S. and Europe for AMKD and ADPKD. Estimates include the global patient population for IgAN and pMN. All estimates reflect the ultimate target patient population; at initial launch, potential indications may be a subset of the total patient population opportunity. The AMKD estimated patient population consists of ~150K patients with AMKD and no other kidney disease-causing comorbidities and ~100K patients with AMKD and other co-morbidities, such as Type 2 diabetes. VX-407 for ADPKD will initially target up to 10% of the patient population.

IgAN: IgA nephropathy; pMN: primary membranous nephropathy; AMKD: APOL1-mediated kidney disease; ADPKD: autosomal dominant polycystic kidney disease

©2026 Vertex Pharmaceuticals Incorporated

Rapid progress across the kidney portfolio

Multiple programs now in mid- and late-stage clinical development



1. Estimated patient population in the U.S. and Europe, unless otherwise noted. 2. IgAN patients continue to be studied in RAINIER. 3. Targets a patient population with a subset of variants in the *PKD1* gene.
IgAN: IgA nephropathy; pMN: primary membranous nephropathy

©2026 Vertex Pharmaceuticals Incorporated

Povetacicept's Phase 3 RAINIER interim analysis supports best-in-class potential in IgAN

Trifecta of efficacy, safety and patient centricity

		VERTEX povetacicept	Otsuka VOYXACT	vera therapeutics TRUTAKNA
Preclinical	**Binding Affinity (K_D)**	**1pM (APRIL), 59 pM (BAFF)**	0.95 pM (APRIL)	33 pM (APRIL), 106 pM (BAFF)
1 Phase 3 Efficacy	**24hr UPCR Reduction (g/g)**	**-52%,** PBO -4%, Diff -50% (Week 36)[1]	-50%, PBO +2%, Diff -51% (Week 40)[2]	-46%, PBO -7%, Diff -42% (Week 36)[3]
	% at KDIGO-Aligned Goal of UPCR <0.5 g/g	**42.4% pts <0.5 g/g** (Week 36)	25.5% pts <0.5g/d (Week 40); 36.7% pts <0.5 g/d (24M)	*Not Reported*
	Gd-IgA1 Reduction	**77.4%** (Week 36)	67.1% (Week 48)	68% (Week 36)
	Hematuria	**85.1%,** PBO 23.4 %, Diff 61.7% Resolution (Week 36)	19.8% had hematuria; PBO 69% had hematuria (Week 48)[4]	81%, PBO 21% Resolution (Week 36)
	eGFR Slope	*Phase 3 pending*	+0.3, PBO -4.2, Diff +4.5 (Week 104)	-0.6, PBO -5.6, **Diff +5.0** (Week 104)
	eGFR Change from Baseline	*Phase 3 pending*	+1.3, PBO -7.9, **Diff +9.2** (Week 104)	−0.1, PBO −5.7, Diff +5.6 (Week 52) −1.8, PBO −12.8, **Diff +11.1** (Week 104)
	Composite Kidney Progression/Failure[5]	*Phase 3 pending*	**97.1%** (Week 104, N=510)	**76%** (Week 104, N=428)
2 Phase 3 Safety[6]	**SAEs vs placebo**	3.0% vs 4.3% PBO	8.1% vs 12.7% PBO	7.0% vs 15.4% PBO
	Serious Infection	0.5% vs 0.5% PBO	1.9% vs 4.0% PBO	2.8% vs 3.7% PBO
	Injection Site Reactions	14.5% vs 2.2% PBO	35.1% vs 32.3% PBO	30.4% vs 7.5% PBO
3 Patient Centricity	**Dosing Frequency**	**Every 4 weeks**	Every 4 weeks	Weekly
	Volume	**0.46 ml**	2 ml	1 ml
	Administration	**Autoinjector**	Pre-filled syringe	Autoinjector

Note: Cross-trial data shown for context only, a H2H comparison cannot be made. 1. Povetacicept PBO adjusted response: 49.8%, 2. VOYXACT PBO adjusted response: 51.2% at week 40. 3. TRUTAKNA PBO adjusted response 42% 4. VOYXACT uses different methodology than pove and TRUTAKNA for hematuria resolution. 5. Each trial has different kidney composite endpoints. 6. Phase 3 safety data represented are from the 36 week interim analysis for povetacicept, from the 24 month final analysis for VOYXACT; and from the final analysis for TRUTAKNA.

©2026 Vertex Pharmaceuticals Incorporated

SAE: Serious Adverse Event; Q4W: Every 4 weeks; Q1W: Every week; AI: Autoinjector; PFS: Pre-filled syringe IA: Interim analysis FA: final analysis

Akinlolu Ojo, M.D., Ph.D., MBA

Executive Dean of the School of Medicine at the University of Kansas
Professor, Nephrology and Hypertension
Professor, Population Health



***Areas of expertise**: Nephrology, chronic kidney disease (CKD), kidney and kidney-pancreas transplantation outcomes, health disparities and global health issues*

Topics:

- Inaxaplin AMPLIFIED Phase 2b trial results
- Inaxaplin AMPLITUDE Phase 2/3 trial
- AMKD patient need

Disclosures: Dr. Ojo is on the steering committee for inaxaplin clinical development and on the AMKD advisory board for Vertex Pharmaceuticals, on the data monitoring committee for AstraZeneca UK, in a research collaboration agreement with Regeneron, a member of the Board of Directors for Arbor Research Collaborative for Health, and a member of the Advisory Panel for Gastroenterology and Urology Devices at the US Food and Drug Administration.

AMPLIFIED data add to evidence base for inaxaplin as potential first- and best-in-class treatment targeting the underlying cause of AMKD

PARAMETER	Cohort 1: Patients with AMKD with modest proteinuria N=22[a]	Cohort 2: Patients with AMKD and Type 2 diabetes N=17[a]
Primary Endpoint (UACR)		
Mean baseline UACR g/g (SD)	0.28 (0.09)	0.67 (0.87)
Geometric mean % change of UACR at Week 13 compared to baseline (95% CI)[b]	-42.7% (-58.3%, -21.1%)[c]	-17.3% (-36.3%, 7.2%)[c]
Other Endpoint (UPCR)		
Mean baseline UPCR g/g (SD)	0.46 (0.20)	1.12 (1.51)
Geometric mean % change of UPCR at Week 13 compared to baseline (95% CI)[b]	-44.7% (-60.9%, -21.9%)[c]	-25.4% (-45.1%, 1.4%)[c]

- Cohort 1 efficacy mirrors that of inaxaplin proof-of-concept Phase 2 study in AMKD patients with FSGS
- Majority of patients in both cohorts did not have FSGS
- Generally safe and well tolerated[d]

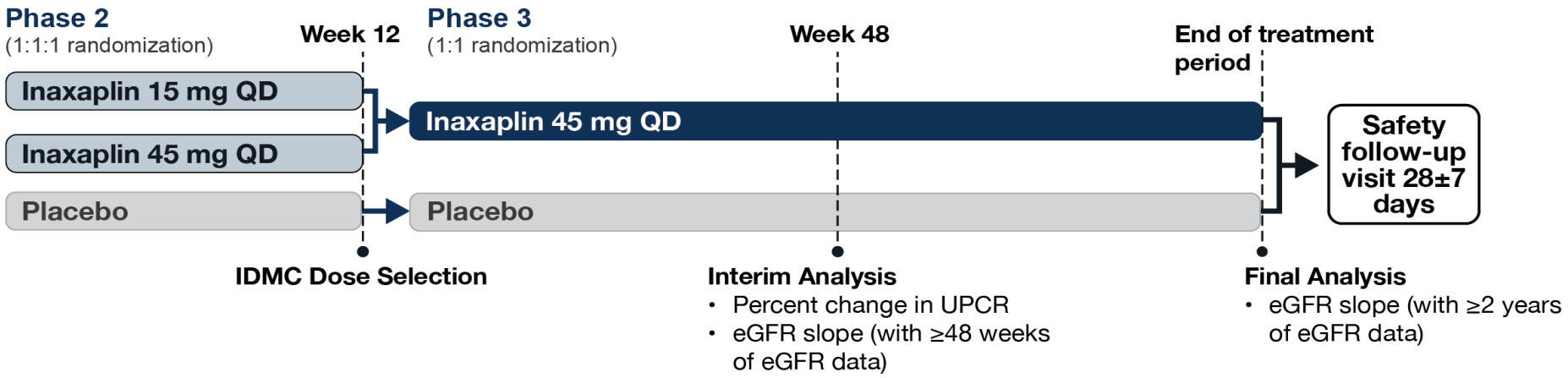
[a]According to the pre-specified statistical analysis plan, two people, one in each cohort, who were noncompliant with treatment were not included in the efficacy analyses; [b]Analyses include those on treatment who had an assessment at Week 13: 18 and 14 people in cohort 1 and 2, respectively; [c]95% CI were generated post-hoc. [d]No serious adverse events (SAEs) related to inaxaplin. All adverse events (AEs) were mild or moderate in severity. Most common AE (occurring in >5% of subjects) was headache (7.3%). Five patients had isolated, asymptomatic transaminase elevations, which resolved.
AMPLIFIED was a Phase 2b multi-cohort, open-label, 13-week trial. Entry criteria: adults 18 - 67 years; BMI of 18.0 to 45.0 kg/m2 and TBW ≥40 Kg; 2 APOL1 high-risk variants; eGFR ≥25 mL/min/1.73m^{2}; SBP ≤180 mmHg and DBP ≤110 mmHg; all subjects had to be on a stable dose of permitted concomitant medications and standard-of-care treatment regimens prior to screening.

AMKD: APOL1-mediated kidney disease; CI: Confidence interval; SD: Standard deviation; UACR: Urine albumin to creatinine ratio; UPCR: Urine protein to creatinine ratio; FSGS: focal segmental glomerulosclerosis

©2026 Vertex Pharmaceuticals Incorporated

AMPLITUDE pivotal trial of inaxaplin in patients with AMKD with severe proteinuria fully enrolled; interim analysis on track for early 2027

Phase 2/3 Study Enrollment Complete With a Total of 522 Patients Enrolled



Note: At the end of treatment, patients have an option to enroll in a long-term open label extension study.

Assessments

Primary endpoints

- **Interim analysis (IA)**
  - Percent change in UPCR from baseline at Week 48
  - eGFR slope (with ≥48 weeks of eGFR data)
- **Final analysis**
  - eGFR slope (with ≥2 years of eGFR data)

Key Eligibility Criteria

Key inclusion criteria:

- Aged 10 to 65 years
- *APOL1* genotype of *G1/G1, G2/G2, G1/G2*
- Proteinuric kidney disease

Key exclusion criteria:

- History of diabetes mellitus
- Uncontrolled hypertension
- Solid organ or bone marrow transplant

©2026 Vertex Pharmaceuticals Incorporated

Clinical perspective

- Large number of patients with AMKD who are not getting treatment
- AMPLIFIED cohort 1: substantial reductions in UACR and UPCR
  AMPLIFIED cohort 2: treatment effect is smaller, given 2 causes of kidney disease
- AMPLIFIED results compelling, consistent in FSGS/non-FSGS patients, on top of standard of care
- AMPLITUDE fully enrolled, looking forward to interim analysis data early 2027

©2026 Vertex Pharmaceuticals Incorporated

Richard Lafayette, M.D.

Professor of Medicine (Nephrology) at the Stanford University Medical Center
Founder and Director of the Stanford Glomerular Disease Center



***Areas of Expertise**: Nephrology, glomerular disease, amyloidosis, kidney and pancreas transplantation, pathogenesis of IgA nephritis*

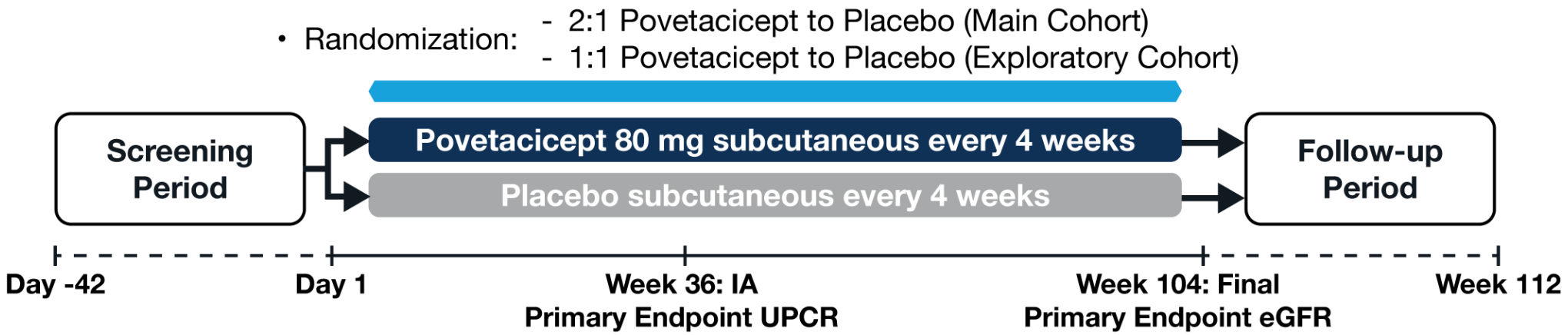
Topics:

- RAINIER pivotal trial

Disclosures: Dr. Lafayette is co-chair of RAINIER steering committee. Has received research support from NIH, UPenn, UMich, Beigene, Biogen, Calliditas, Travere, Vera, Roche, Alexion, Otsuka and is a consultant for Amgen, Alexion, Biogen, Calliditas, Otsuka, Travere, Takeda and Vera.

RAINIER is an ongoing, global, Phase 3 randomized, double-blind, placebo-controlled trial evaluating povetacicept in adults with IgA Nephropathy

Largest contemporary trial for the treatment of IgAN



Key Eligibility Criteria

- Adults with biopsy confirmed IgAN
- UPCR ≥0.75 g/g or UPE ≥1.0 g/day
- eGFR ≥30 mL/min/1.73 m^2 (main cohort)
- Maximal ACEi/ARB ≥12 weeks
- Stable SGLT2i, MRA, or ERA ≥12 weeks (optional)

Treatment

- 557 participants in main cohort randomized 2:1 to:
  - Povetacicept 80 mg SC Q4W; N = 371
  - Placebo; N = 186
- Interim Analysis: 199 subjects at Week 36
  - Povetacicept; N = 131
  - Placebo; N = 68
- Study duration: 2 years with option to enroll in OLE

Assessments

Interim Analysis Primary endpoint:

- Change from baseline in 24-hour UPCR at Week 36

Interim Analysis Secondary Endpoints:

- Change from baseline in Gd-IgA1 at Week 36
- Hematuria Resolution at Week 36

Final Analysis Primary Endpoint

- Total eGFR slope through Week 104

©2026 Vertex Pharmaceuticals Incorporated
Note: ClinicalTrials.gov ID: NCT06564142; data cutoff date 16 January 2026

Enrollment demographics: Participants received optimized standard-of-care therapy at baseline, including ACEi/ARB and SGLT2i

Parameter	Povetacicept 80 mg SC Q4W N = 131	Placebo N = 68
Age; mean (SD) yr	44.1 (12.5)	42.5 (11.8)
Male; n (%)	76 (58.0)	42 (61.8)
Race (Asian/White/Other); n (%)	82 (62.6) / 47 (35.9) / 2 (1.5)	40 (58.8) / 26 (38.2) / 2 (2.9)
Region (APAC/Europe + Middle East/North America); n (%)	76 (58.0) / 31 (23.7) / 24 (18.3)	41 (60.3) / 17 (25.0) / 10 (14.7)
Time since initial biopsy; mean (SD) yr	4.2 (4.2)	4.9 (4.4)
24-hr UPCR; mean (SD) g/g	1.5 (0.9)	1.6 (1.4)
eGFR; mean (SD) mL/min/1.73 m^2	74.4 (30.3)	68.4 (29.5)
Gd-IgA1; mean (SD) ng/mL	6591.7 (4682.1)	6169.7 (4589.0)
Hematuria moderate or large; n (%)	67 (51.1)	36 (52.9)
Prior immunosuppression for IgAN; n (%)	17 (13.0)	10 (14.7)
Any proteinuria lowering medication at baseline; n (%)	130 (99.2)	68 (100)
ACEi/ARB; n (%)	127 (96.9)	67 (98.5)
SGLT2i; n (%)	88 (67.2)	43 (63.2)
MRA; n (%)	19 (14.5)	8 (11.8)
ETA; n (%)	2 (1.5)	2 (2.9)

©2026 Vertex Pharmaceuticals Incorporated

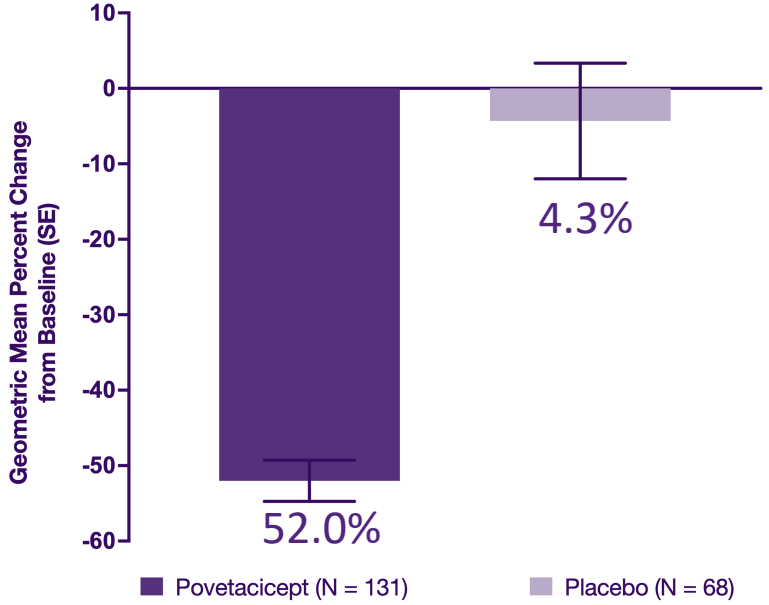
Note: data cutoff date 16 January 2026

PRIMARY ENDPOINT: Statistically significant and clinically meaningful reduction in 24-hour UPCR at Week 36 with povetacicept

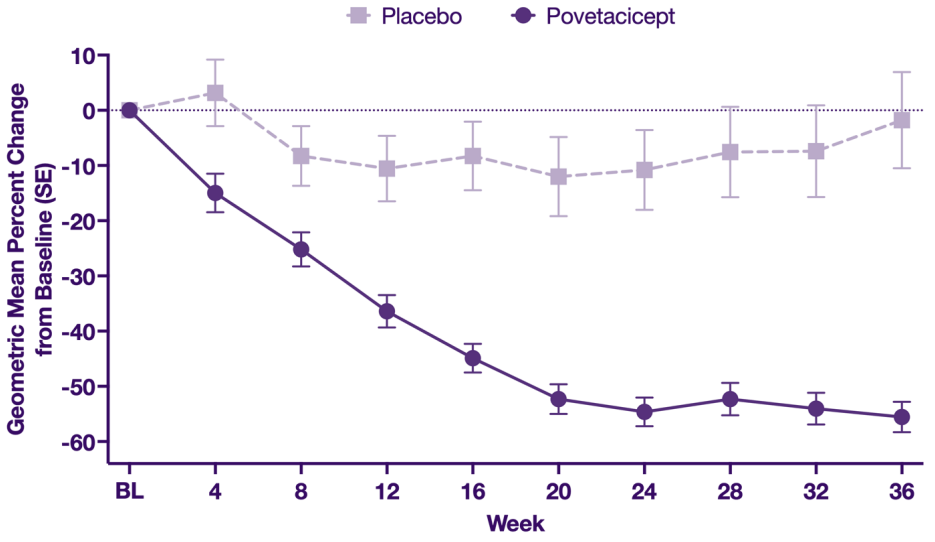
RAINIER™ Ph 3 IgAN

Treatment with povetacicept led to rapid, substantial, and sustained reduction in proteinuria

PRIMARY ENDPOINT: Percent Change from Baseline in 24-hour UPCR at Week 36



Percent Change from Baseline to Week 36 in Spot UPCR



N (Placebo)=	65	63	65	61	62	61	63	61	61	62
N (Povetacicept)=	130	129	128	128	127	128	125	128	129	128

Substantial reductions in 24-hour UPCR with povetacicept

- **52.0% decrease** from baseline **with povetacicept at Week 36**
- **Povetacicept treatment effect at Week 36: 49.8%** (95% CI: 39.2%, 58.6%); ***P* <0.0001**

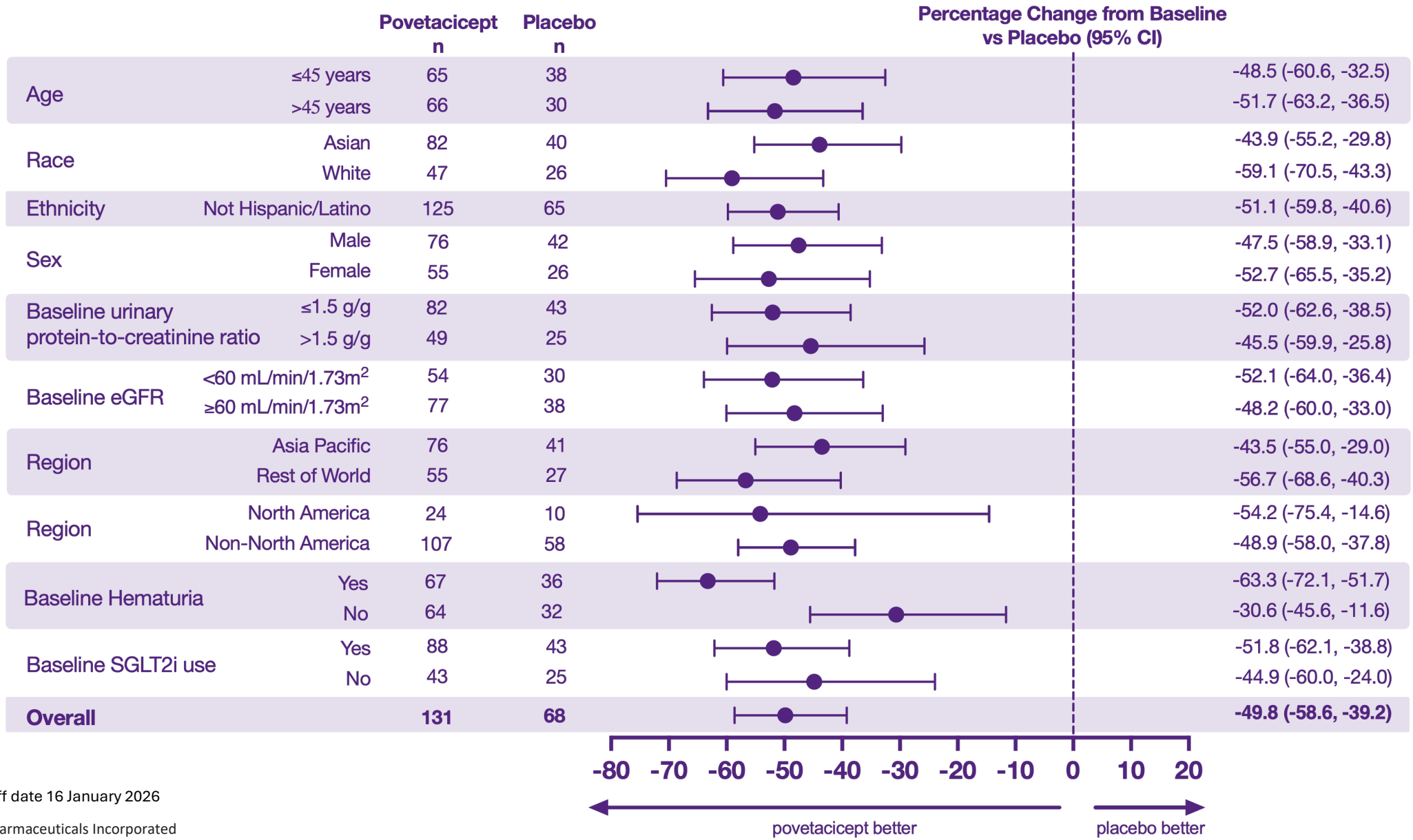
Rapid reduction in spot UPCR with povetacicept

- **Improvement in proteinuria seen as early as week 4**
- **Clear separation between povetacicept and placebo through Week 36**

©2026 Vertex Pharmaceuticals Incorporated
Note: data cutoff date 16 January 2026

Povetacicept treatment effect is consistent across all subgroups

Including North America subgroup



Note: data cutoff date 16 January 2026

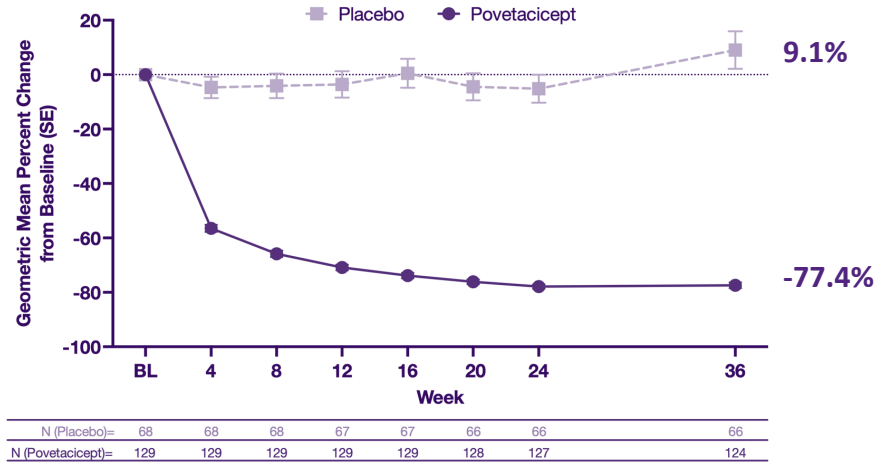
©2026 Vertex Pharmaceuticals Incorporated

Rapid, sustained, statistically significant and clinically meaningful improvement in both secondary endpoints

RAINIER Ph 3 IgAN

Gd-IgA1

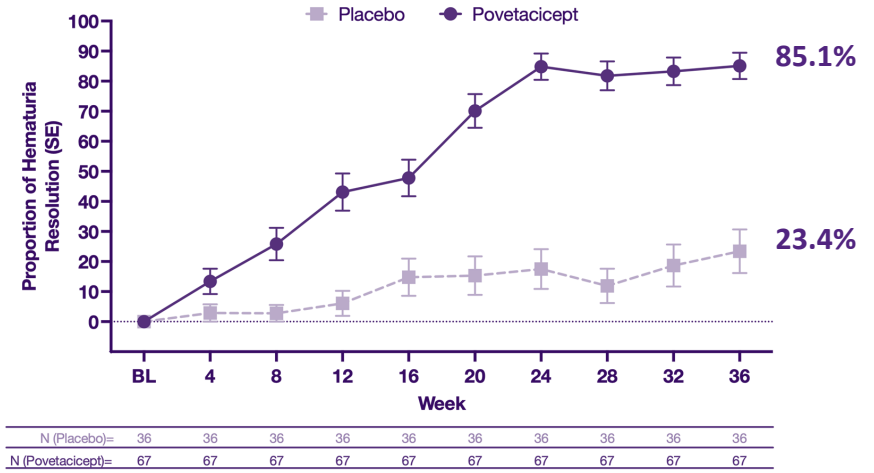
Secondary endpoint: Percent Change from Baseline to Week 36 in Gd-IgA1



- **Rapid reduction** in Gd-IgA1 with povetacicept:
  - **56.5% decrease** from baseline with **povetacicept** and 4.7% decrease with **placebo** at Week 4
- **Reduction continued** to improve through Week 36
  - **77.4% decrease** from baseline with **povetacicept** and 9.1% increase from baseline with **placebo** at Week 36
- **Placebo-adjusted** change from baseline: **79.3%**
  - 95% CI: -82.2, -75.9), P<0.0001

Hematuria

Secondary endpoint: Proportion of Participants Who Achieved Hematuria Resolution through Week 36



Among participants with hematuria at baseline

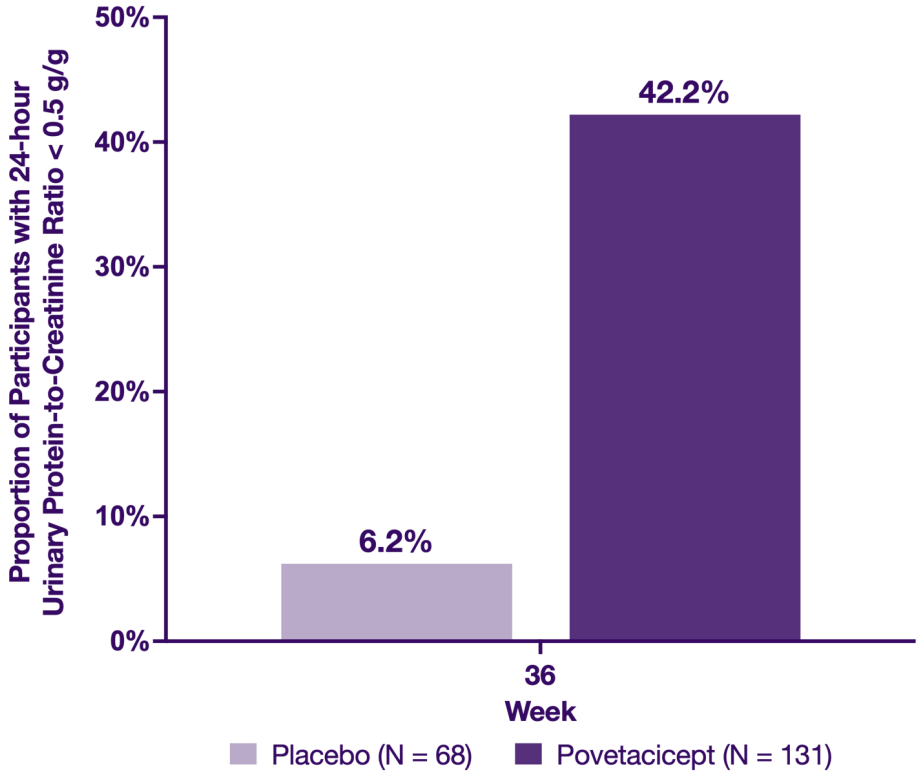
- Hematuria resolved in **85.1%** with **povetacicept** and 23.4% with **placebo** at Week 36
- **Placebo-adjusted** change from baseline: **61.7%**
  - 95% CI: 44.9, 78.4), P<0.0001
- Hematuria resolution occurred **rapidly**
  - Median time to first hematuria resolution was **13 weeks** with **povetacicept**

©2026 Vertex Pharmaceuticals Incorporated

Clinically meaningful reduction in 24-hour UPCR <0.5 g/g and <0.3 g/g at Week 36 with povetacicept

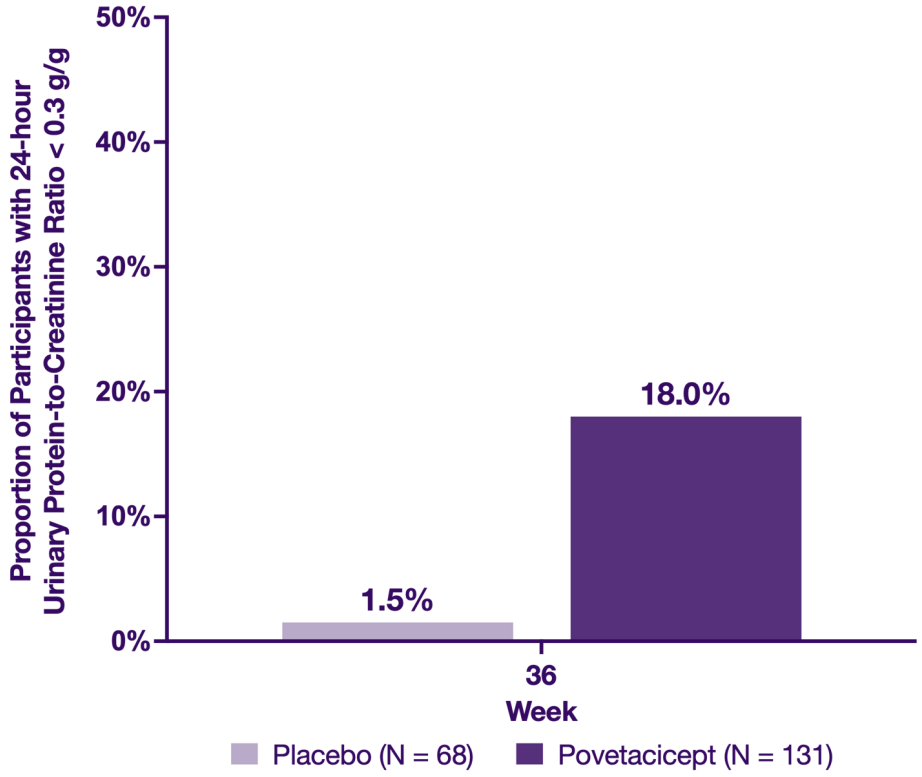
42.2% Achieved KDIGO-aligned goal of UPCR <0.5 g/g

(A) Proportion of Participants with 24-hour UPCR <0.5 g/g through Week 36



Proportion of participants who achieved **24-hour UPCR <0.5 g/g 42.2% with povetacicept** and 6.2% with placebo at Week 36 (nominal p value < 0.0001 for treatment difference)

(B) Proportion of Participants with 24-hour UPCR <0.3 g/g through Week 36



Proportion of participants who achieved **24-hour UPCR <0.3 g/g 18.0% with povetacicept** and 1.5% with placebo at Week 36 (nominal p value = 0.001 for treatment difference)

©2026 Vertex Pharmaceuticals Incorporated
Note: data cutoff date 16 January 2026

Povetacicept was generally safe and well tolerated

Parameter	Povetacicept N =372 n (%)	Placebo N =185 n (%)
Any AE	279 (75.0)	145 (78.4)
Grade 1/mild	153 (41.1)	84 (45.4)
Grade 2/moderate	115 (30.9)	53 (28.6)
Grade 3/severe	11 (3.0)	8 (4.3)
AE of Infection	171 (46.0)	75 (40.5)
Grade 1/mild	105 (28.2)	43 (23.2)
Grade 2/moderate	64 (17.2)	31 (16.8)
Grade 3/severe	2 (0.5)	1 (0.5)
Related/Possibly Related AEs	117 (31.5)	37 (20.0)
Events occurring in ≥10% of participants in either treatment group		
Upper respiratory tract infection	68 (18.3)	21 (11.4)
Nasopharyngitis	36 (9.7)	23 (12.4)
Injection site reactions*	54 (14.5)	4 (2.2)
Any SAE	11 (3.0)	8 (4.3)
SAE of infection	2 (0.5)	1 (0.5)
Any AE leading to treatment discontinuation	1 (0.3)	4 (2.2)
Any AE leading to death	0	0

- Most AEs were **mild to moderate**
- Incidence of AEs and SAEs was **similar between povetacicept and placebo**
- **Low incidence** of AEs **leading to discontinuation;** none due to infection
- **No SAEs related** to povetacicept
- **Most infections were mild or moderate**; incidence of **serious infections** was **balanced**; no opportunistic infections
- **Injection site reactions were mild or moderate** and none led to discontinuation

©2026 Vertex Pharmaceuticals Incorporated
Note: data cutoff date 16 January 2026; * Injection-site reactions were identified according to a prespecified set of preferred terms (including, for example, injection-site reaction and injection-site erythema).

Conclusions

- **Povetacicept treatment led to rapid, sustained, statistically significant, and clinically meaningful improvements across multiple outcome measures in IgA nephropathy**

- **52.0% reduction in 24-hour UPCR (49.8%** placebo-adjusted) at Week 36 (*P* <0.0001)
  - UPCR reduction **as early as Week 4**
  - **Benefit consistent across all subgroups, including North America subgroup**
  - **42.2%** and **18.0%** of participants achieved **UPCR <0.5 g/g or <0.3 g/g**

- **77.4% reduction in Gd-IgA1 (79.3%** placebo-adjusted) at Week 36 (*P* <0.0001)
  - Gd-IgA1 reduction **as early as Week 4**

- **Hematuria resolved in 85.1%** (**61.7%** placebo-adjusted) at Week 36 (*P* <0.0001)
  - Median time to first resolution with povetacicept was **13 weeks**

- Povetacicept was generally **safe and well tolerated** with a **similar incidence** of AEs and SAEs **to placebo**

- Povetacicept treatment offers **Q4W SC dosing**, with **small volume autoinjector** for **self-administration (<0.5 mL,** 27G needle)

For patients with IgAN, povetacicept offers transformational efficacy with disease-modifying potential, along with favorable safety and patient-centric administration features

©2026 Vertex Pharmaceuticals Incorporated

RAINIER
Ph 3 IgAN

RAINIER data were just published in the ***New England Journal of Medicine*** **TODAY**

RAINIER data will be presented in the late-breaking research session tomorrow, **October 24, 4:30 - 6:00 pm**
(Four Seasons Ballroom 2)

©2026 Vertex Pharmaceuticals Incorporated



Q&A Session

©2026 Vertex Pharmaceuticals Incorporated



Kidney Program Updates at the American Society of Nephrology Kidney Week 2026

October 23, 2026

Presentation intended for the investment community

©2026 Vertex Pharmaceuticals Incorporated