Kidney Program Updates at the American Society of Nephrology Kidney Week 2025

November 8, 2025

Presentation intended for the investment community

Agenda

Welcome

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

Kidney portfolio

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

RUBY-3 late breaking data recap

James A. Tumlin, M.D., Professor of Medicine in Nephrology at Emory University School of Medicine, Director of Research at Georgia Nephrology, President of NephroNet

RAINIER Phase 3 study

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

The role of guidelines in shaping the standard of care

Brad Rovin, M.D., Director, Division of Nephrology, Vice Chair of Research, Professor of Internal Medicine, Ohio State University Wexner Medical Center

Q&A Session

Reshma Kewalramani, Dr. Tumlin, Dr. Lafayette, Dr. Rovin

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 the kidney 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, plans to complete discussions with FDA regarding advancement of gMG into pivotal development, expectations for wAIHA Phase 2 study data, plans for potential U.S. accelerated approval for povetacicept in IgAN, including plans to initiate rolling BLA submission by year end 2025 and to complete the submission in H1:2026, and expectations for completion of enrollment in the AMKD AMPLIFIED study in Q4 2025 and for an interim analysis in the AMKD AMPLITUDE study in Q4 2026 for potential U.S. accelerated approval. 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 development programs may not support registration or further development of its potential medicines due to safety, efficacy or other reasons, that the company may be unable to make the anticipated regulatory submissions on the expected timeline, or at all, 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.

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

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

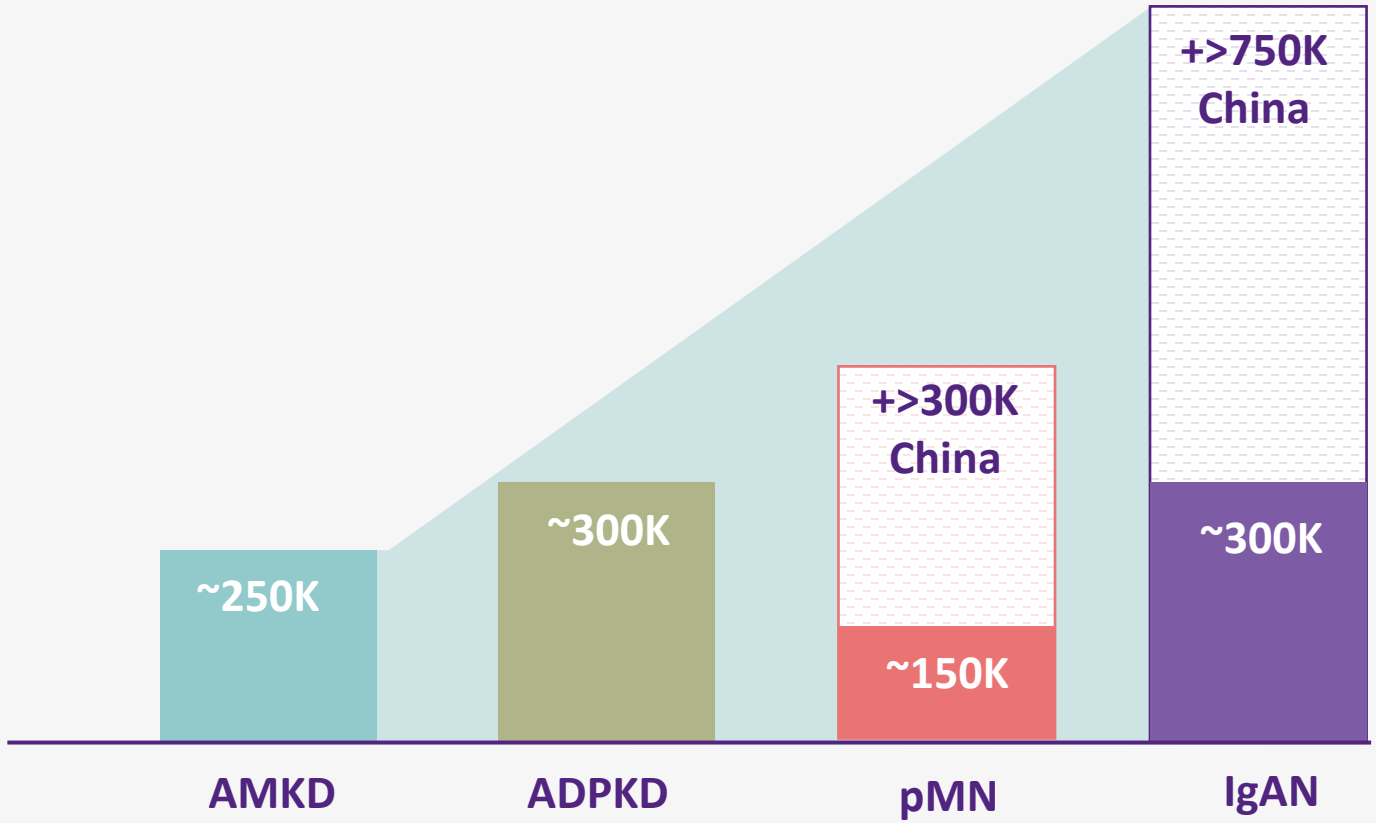
Rapid progress across the kidney portfolio with multiple programs now in mid- and late-stage clinical development

		PATIENTS[1]	RESEARCH	PHASE 1	PHASE 2	PHASE 3	APPROVED	
B cell driven renal diseases	Povetacicept – IgAN[2]	~300K (>750K China)			RAINIER			*Rolling BLA submission for AA to begin YE 2025 Full trial enrolled*
	Povetacicept – pMN	~150K (>300K in China)			OLYMPUS			*Phase 2/3 pivotal trial initiated*
	Additional B cell mediated diseases[3]	TBD						
APOL1-mediated kidney disease (AMKD)	Inaxaplin – Primary AMKD	~150K			AMPLITUDE			*IA cohort enrollment complete*
	Inaxaplin – AMKD with moderate proteinuria or diabetes	~100K		AMPLIFIED				*On track to complete enrollment by YE '25*
Autosomal dominant polycystic kidney disease	VX-407[4]	Up to ~30K			aglow Clinical Study			*Proof-of-concept study underway*
	Serial innovation to reach all ADPKD patients	~300K (incl. 30K)						

1. Estimated patient population in the U.S. and Europe, unless otherwise noted. 2. IgAN patients continue to be studied in RUBY-3 3. Multiple programs in various phases. 4. Targets a patient population with a subset of variants in the *PKD1* gene.
IgAN: IgA nephropathy; pMN: primary membranous nephropathy.

High unmet need + large patient populations = significant opportunity

Vertex seeks to be a leader in the renaissance in renal medicine



ULTIMATE ADDRESSABLE PATIENT POPULATION*

3
programs in pivotal development

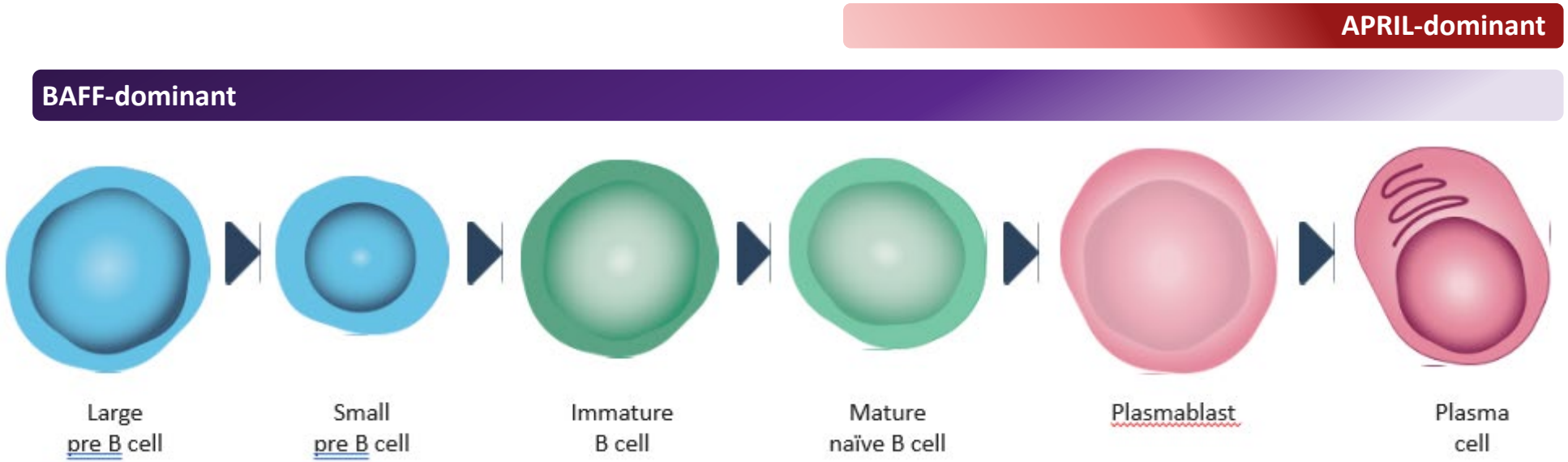
4
potential kidney launches by 2030

>$B
each disease area represents a multi-$B opportunity

*Epidemiological estimates include patients in the U.S. and Europe for AMKD, and ADPKD. Estimates include patients in Asia 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. VX-407 for ADPKD will initially target up to 10% of the patient population.

BAFF and APRIL are central to pathogenesis of B cell driven diseases

Inhibiting both BAFF and APRIL provides optimal B cell control



BAFF

- Important in early B cell development
- Promotes plasma cell survival and activity; regulates early pathogenic B cell development
- Exerts additional benefits on pathogenically activated T and innate immune cells, kidney mesangial cells and podocytes

APRIL

- Important in later B cell functioning
- Limited to promoting the survival of plasma cells

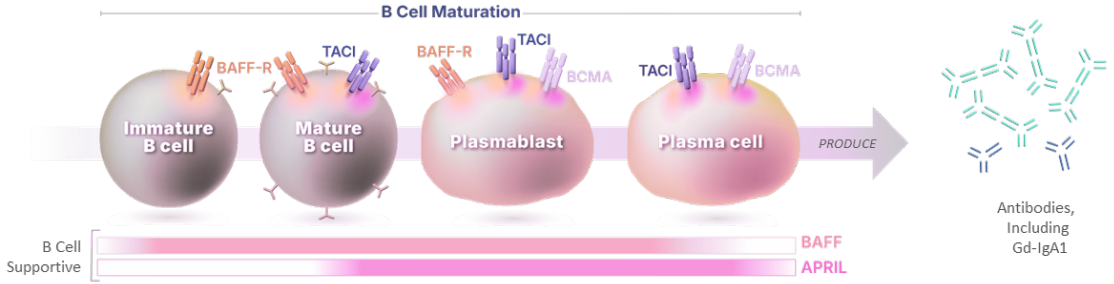
Pove: dual BAFF + APRIL inhibitor, specifically engineered for optimal B cell control

Plus significant advantages that yield desirable, patient-centric features

Specifically engineered for

- ✓ High affinity for BAFF + APRIL
- ✓ High potency
- ✓ High tissue distribution, notably to the kidney

By inhibiting both BAFF and APRIL, pove is designed to control B cells across the continuum of B cell development and maturation

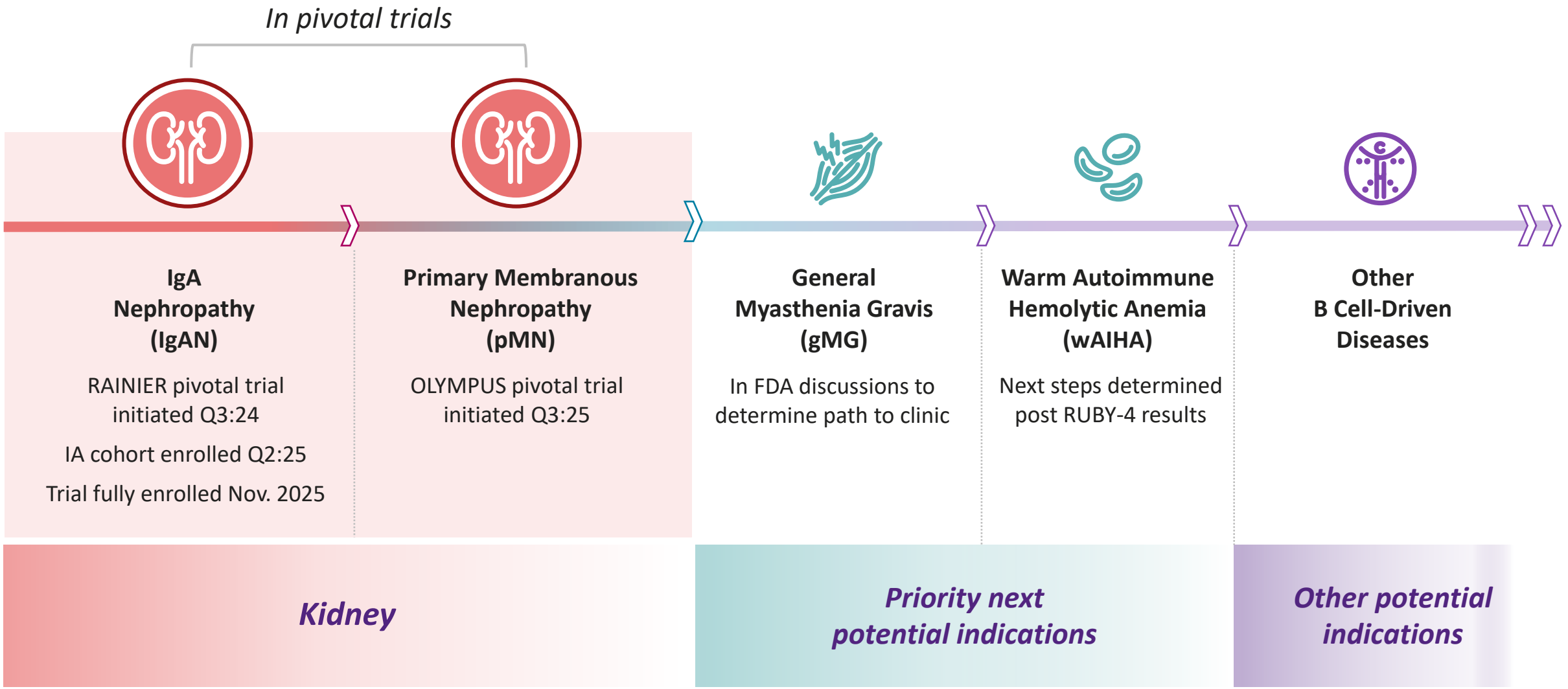


Desirable, patient-centric features and differentiated dosing

- ✓ At-home administration
- ✓ Subcutaneous auto-injector
- ✓ Every four weeks
- ✓ Small volume (<0.5 mL)

Pove is the only dual BAFF + APRIL inhibitor in pivotal development for multiple renal diseases

Povetacicept is delivering on its pipeline-in-a-product potential



IgAN: RAINIER Phase 3 trial fully enrolled in ~15 months
Fastest of any contemporary IgAN trial

RUBY-3
IgAN and pMN

Phase 2 continues to show best-in-class clinical potential

RAINIER

IA cohort, for potential U.S. accelerated approval, enrolled Q2:25
Phase 3 trial now fully enrolled

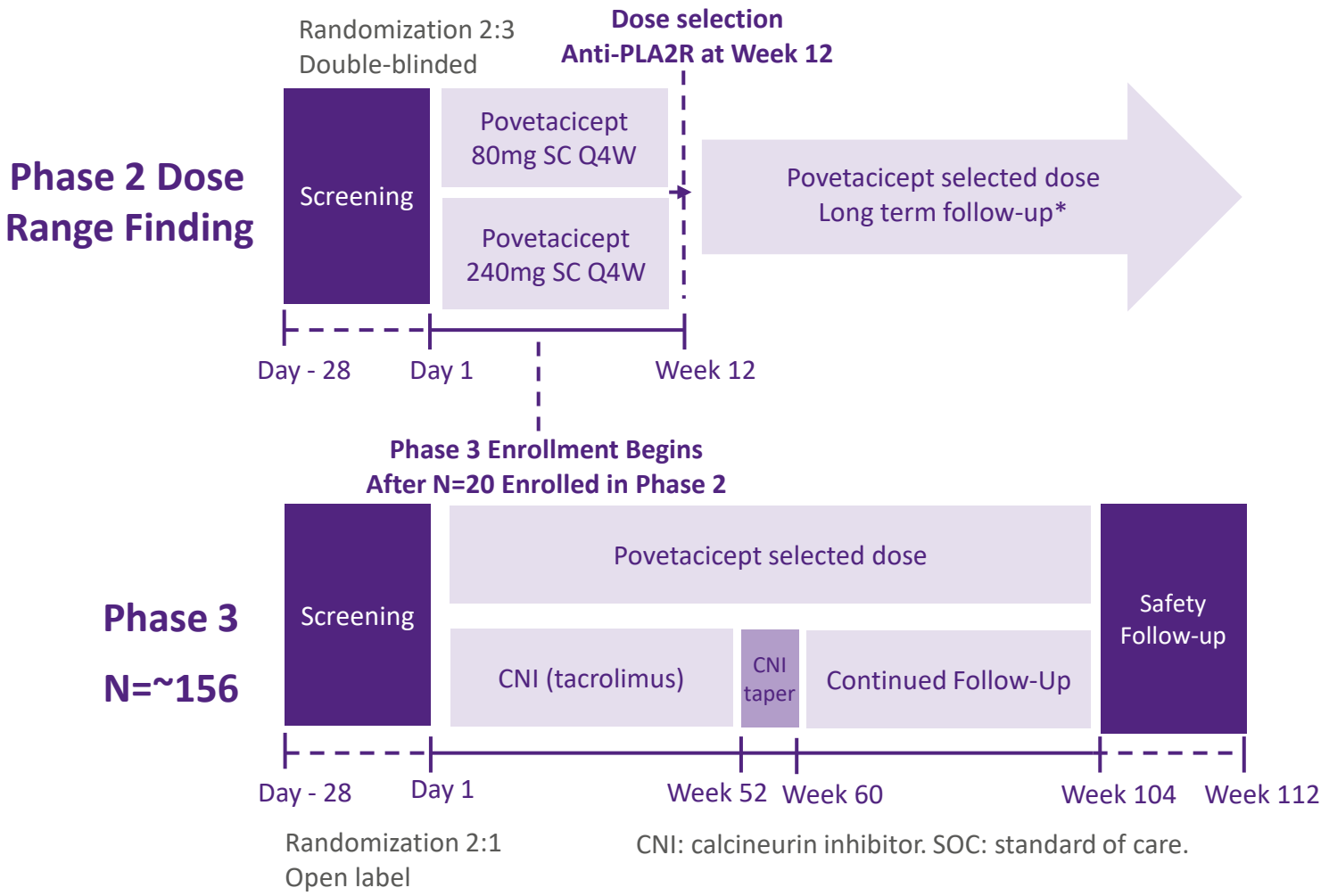
FDA Breakthrough Therapy Designation and rolling review secured

Vertex to initiate rolling BLA submission by year end 2025
On track to complete submission in H1:2026 for potential U.S. AA
VRTX Priority Review Voucher ensures 6-month FDA review

IA: interim analysis. AA: accelerated approval.

pMN: Pove is the first BAFF/APRIL inhibitor in pivotal development

Single adaptive Phase 2/3 study of povetacicept versus SOC



CNI: calcineurin inhibitor. SOC: standard of care.

**Subjects dosed through Week 104 and then have Safety Follow-Up through Week 112*

Population:

- Adults with pMN diagnosis by biopsy
- UPCR ≥3.5 g/g
- eGFR: ≥40 mL/min/1.73 m^2
- Stable doses of best supportive care (e.g., RAASi, SGLT2i) for ≥12 weeks

Primary Endpoint (Phase 3):

- Proportion of subjects with complete clinical remission at 104 wks[(1)]

Secondary Endpoints (Phase 3):

- Proportion of subjects with complete clinical remission at 104 wks[(2)]
- Proportion of subjects with overall clinical remission at 104 wks[(3)]

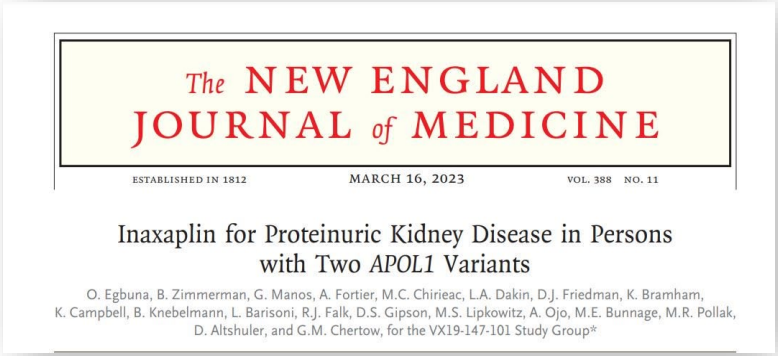
Fast track designation by FDA
PRIME designation by EMA

[(1)]Defined as 24-hour UPCR <0.5 g/g and stable eGFR (≤15% reduction from baseline)
[(2)]Defined as 24-hour UPCR <0.3 g/g and stable eGFR (≤15% reduction from baseline)
[(3)]Defined as 24-hour UPCR <3.5 g/g and ≥50% reduction from baseline; stable eGFR

AMKD: Leading the way with inaxaplin for patients with significant unmet need

On track to achieve major milestones over the next 12 months

First and only drug to achieve proof of concept in AMKD



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 16, 2023 VOL. 388 NO. 11

Inaxaplin for Proteinuric Kidney Disease in Persons with Two *APOL1* Variants

O. Egbuna, B. Zimmerman, G. Manos, A. Fortier, M.C. Chirieac, L.A. Dakin, D.J. Friedman, K. Bramham, K. Campbell, B. Knebelmann, L. Barisoni, R.J. Falk, D.S. Gipson, M.S. Lipkowitz, A. Ojo, M.E. Bunnage, M.R. Pollak, D. Altshuler, and G.M. Chertow, for the VX19-147-101 Study Group*

Innovation recognized by global regulatory agencies

FDA

- Breakthrough Therapy Designation*
- Rare Pediatric Disease Designation*

EMA

- Orphan Drug Designation
- Priority Medicines Scheme (PRIME)

On track for major milestones

Sept 2025

Completed enrollment of IA cohort

AMPLITUDE

Q4 2025

Target to complete enrollment

AMPLIFIED

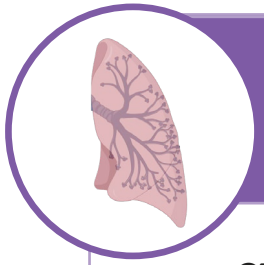
Q4 2026

Interim analysis at 48 weeks for potential U.S. accelerated approval

AMPLITUDE

*For APOL1-mediated FSGS

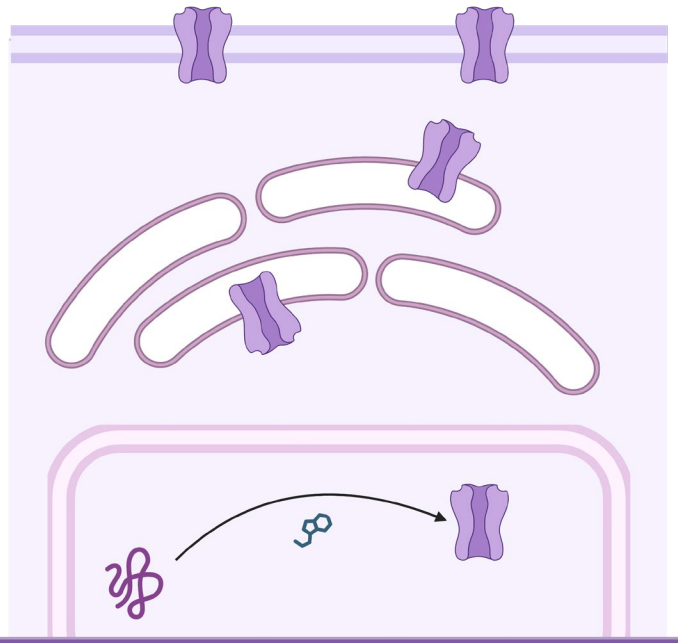
ADPKD: Leveraging our CF expertise and seeking to transform patient lives through protein correction and serial innovation



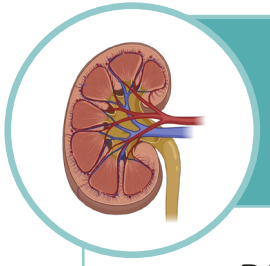
Cystic fibrosis

kalydeco® ORKAMBI® symdeko® trikafta® alyftrek™

CFTR correctors promote proper folding of CFTR and restore trafficking to the cell surface



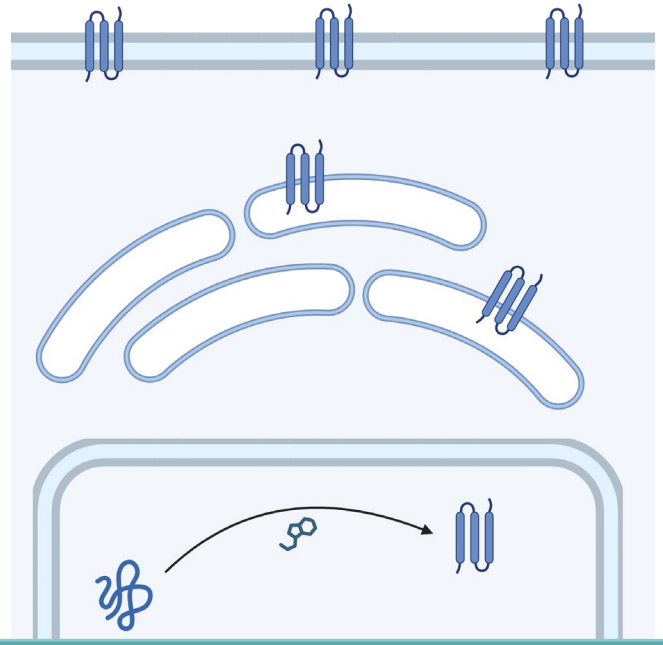
KALYDECO addressable population in U.S.: ~4%
TRIKAFTA & ALYFTREK in U.S.: ~95%



ADPKD

First asset VX-407 in Phase 2 POC

PC1 correctors aim to promote proper folding and restore trafficking to the cell surface



VX-407 addressable population: up to ~10%

VX-407 targets a subset of variants in the PKD1 gene, estimated at up to ~30,000 (or up to ~10%) of the overall patient population in the U.S. and Europe

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:

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#SA-OR091

Efficacy and Safety of Povetacicept in IgA Nephropathy and Primary Membranous Nephropathy at 48 Weeks of Treatment (RUBY-3 Study)

James Tumlin[1]; Rajesh Yalavarthy[2]; Dong Ki Kim[3]; Ju-Young Moon[4]; Inwhee Park[5]; Sung Gyun Kim[6]; Sreedhar Mandayam[7]; Frank Cortazar[8]; Amanda Enstrom[9]; Heather Thomas[9]; Jiahua Li[9], Yih-Chieh Chen[9]; Stanford Peng[9]; Jason Sanders[9]; Ogo Egbuna[9]; Arvind Madan[10]

[1]NephroNet Clinical Trials Consortium and Emory University School of Medicine, Atlanta, GA, USA; [2]Western Nephrology, Arvada, CO, USA; [3]Seoul National University Hospital, Seoul, Republic of Korea; [4]Kyung Hee University Hospital at Gangdong, Seoul, Republic of Korea; [5]Ajou University School of Medicine, Suwon-si, Republic of Korea; [6]Hallym University Sacred Heart Hospital, Anyang-si, Republic of Korea; [7]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [8]New York Nephrology Vasculitis and Glomerular Center, Albany, NY, USA; [9]Vertex Pharmaceuticals Incorporated, Boston, MA, USA; [10]Central Florida Kidney Specialists, Orlando, FL, USA

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08 November 2025, Houston, TX USA

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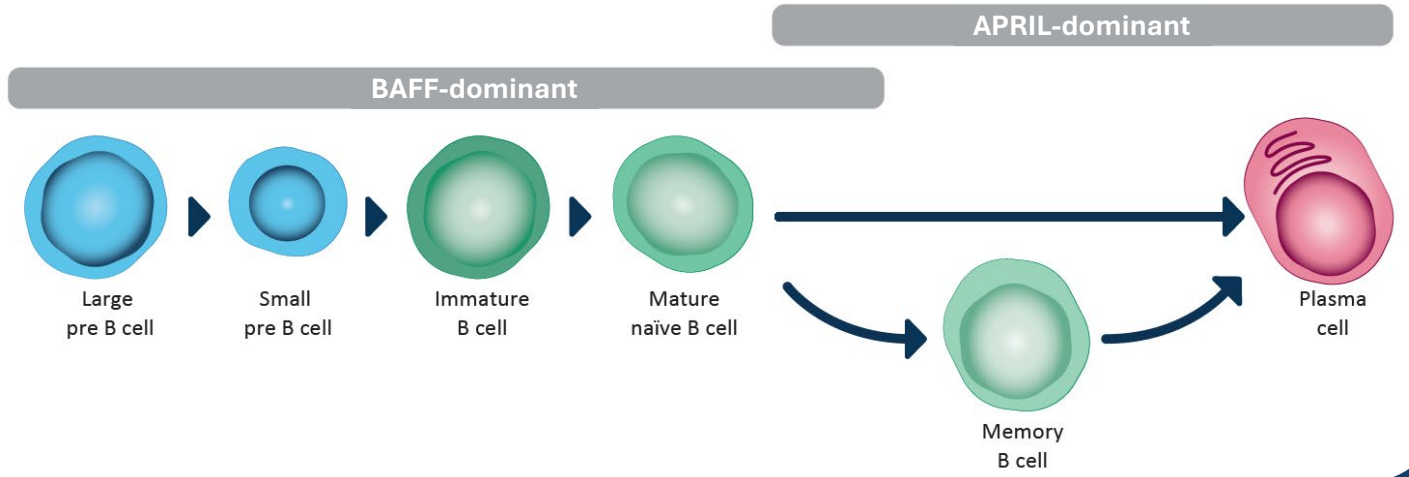
Consultant or Expert Testimony	• Alexion • Amgen • Argenyx • AstraZeneca • Aurnia Pharmaceuticals • BION International	• Calliditas Therapeutics • HIBAR Microsciences LLC • Lilly • Mallinckrodt Pharmaceuticals • NephroNet Clinical Trials Consortium • Novartis	• Novo Nordisk (Chinook) • Relypsa • Travere Therapeutics • Vera Therapeutics • Vertex Pharmaceuticals (Alpine Immune Sciences)
Patents or Royalties	• HIBAR Microsciences LLC	• Tempest Therapeutics	• University of California
Advisory or Leadership Role	• Achillion Pharmaceuticals • Alexion • Aurinia Pharmaceuticals • Bayer • Calliditas Therapeutics	• ChemoCentryx • Epizon Pharma • Florida Society of Nephrology • Gilead Sciences • KBP Biosciences	• Natera • Novartis • Relypsa • Vera Therapeutics
Stock/Stock Options	• Coremedix	• Vertex Pharmaceuticals	

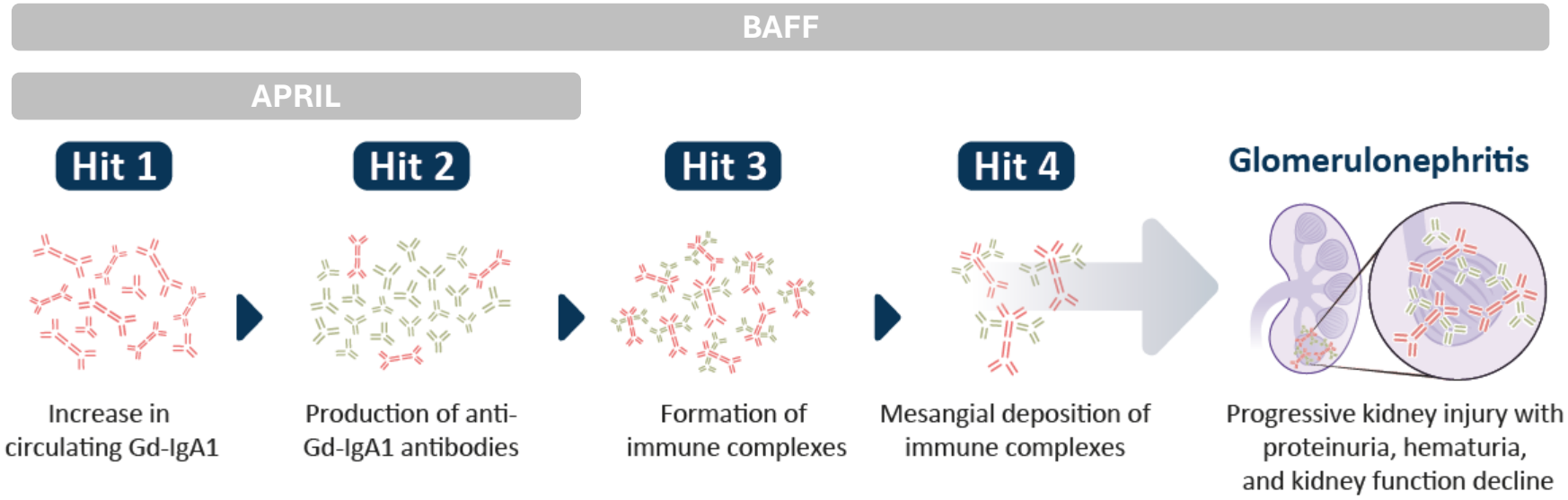
BAFF + APRIL: Central to the Pathogenesis of Autoimmune Glomerulonephritis

- **BAFF** primarily regulates earlier B cell stages; and promotes pathogenic T and innate immune cells, aberrant IgA glycosylation leading to Gd-IgA1 (IgAN), pathogenic autoantibodies against PLA2R (pMN), as well as mesangial cell proliferation and podocyte injury.
- **APRIL** primarily regulates plasma cells.



IgAN Pathogenesis

In the 4-hit hypothesis, **APRIL** primarily promotes pathogenic antibody formation (Hits 1 & 2), while **BAFF** promotes disease across the entire pathogenic spectrum.



Source: Cheung CK et al. *Front Nephrol.* 2024;1(3)1346769

Povetacicept is a Dual BAFF + APRIL Inhibitor Engineered for Superior Potency, Affinity, and Enhanced Tissue Distribution

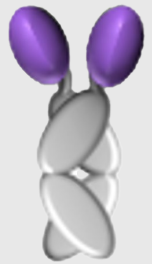
WT-TACI Fc

- Modest BAFF, weak APRIL potency
- Modest BAFF binding affinity
- Moderate tissue distribution

WT-TACI Fc	Potency IC_{50} (nM)	Binding Affinity K_d (s^{-1})
BAFF	20.8	8.63×10^{-5}
APRIL	>200	Could not be determined
BAFF + APRIL	>200	---

Directed Evolution

Povetacicept



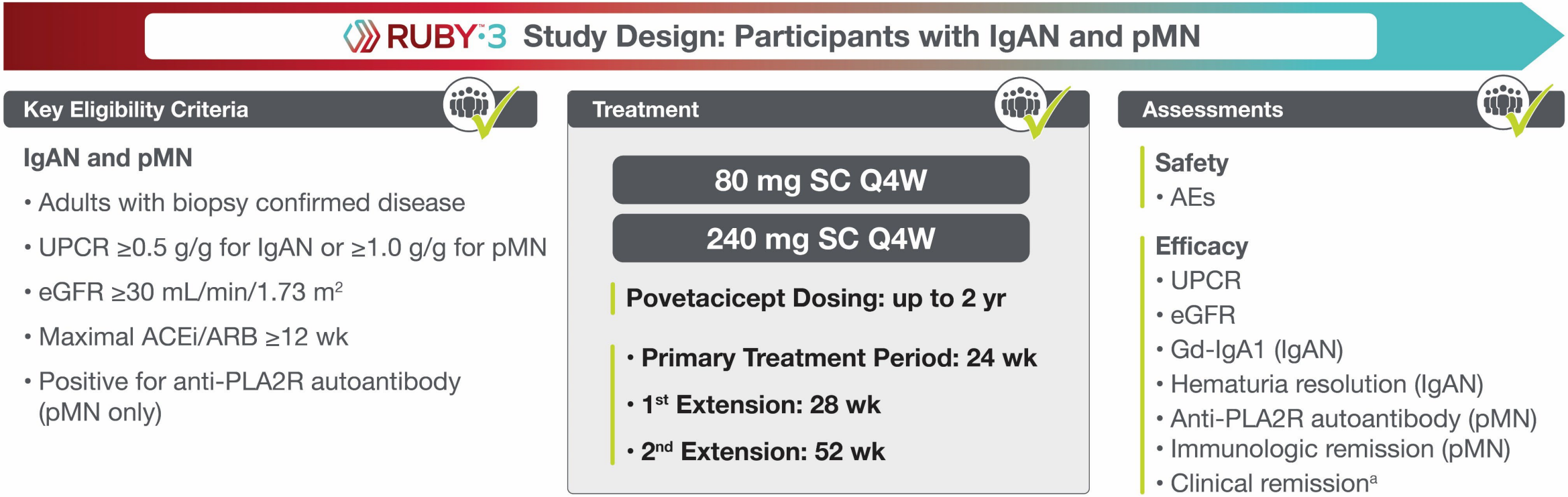
- Superior potency against BAFF and APRIL
- Superior BAFF and APRIL binding affinity
- Enhanced biodistribution across various tissues compared to WT-TACI Fc, with higher relative distribution in the kidney

WT-TACI Fc	Potency IC_{50} (nM)	Binding Affinity K_d (s^{-1})
BAFF	1.4	3.67×10^{-5}
APRIL	3.8	7.0×10^{-3}
BAFF + APRIL	3.1	---

Povetacicept represents a significant therapeutic advancement by **targeting the root cause** of autoimmune glomerulonephritis.

Note: Enhanced tissue distribution data on file, not shown.
Source: Evans et al (2023) Arthritis Rheumatol doi: 10.1002/art.42462

RUBY-3 Study Design



Ongoing **Phase 1/2 open-label study in adults** with IgAN and pMN receiving povetacicept

- **IgAN: 80 mg** (N=21 dosed; N=17 at Week 48) or **240 mg** (N=33 dosed; N=30 at Week 48)
- **pMN: 80 mg** (N=10 dosed; N=5 at Week 48)

Note: ClinicalTrials.gov ID: NCT05732402; date of data cut is 13 June 2025

[a] In IgAN, clinical remission is defined as UPCR <0.5 g/g, negative hematuria, and <25% reduction in eGFR versus baseline. In pMN, complete clinical remission is defined as UPCR <0.5 g/g and partial clinical remission is defined as UPCR <3.5 g/g and >50% reduction from baseline.

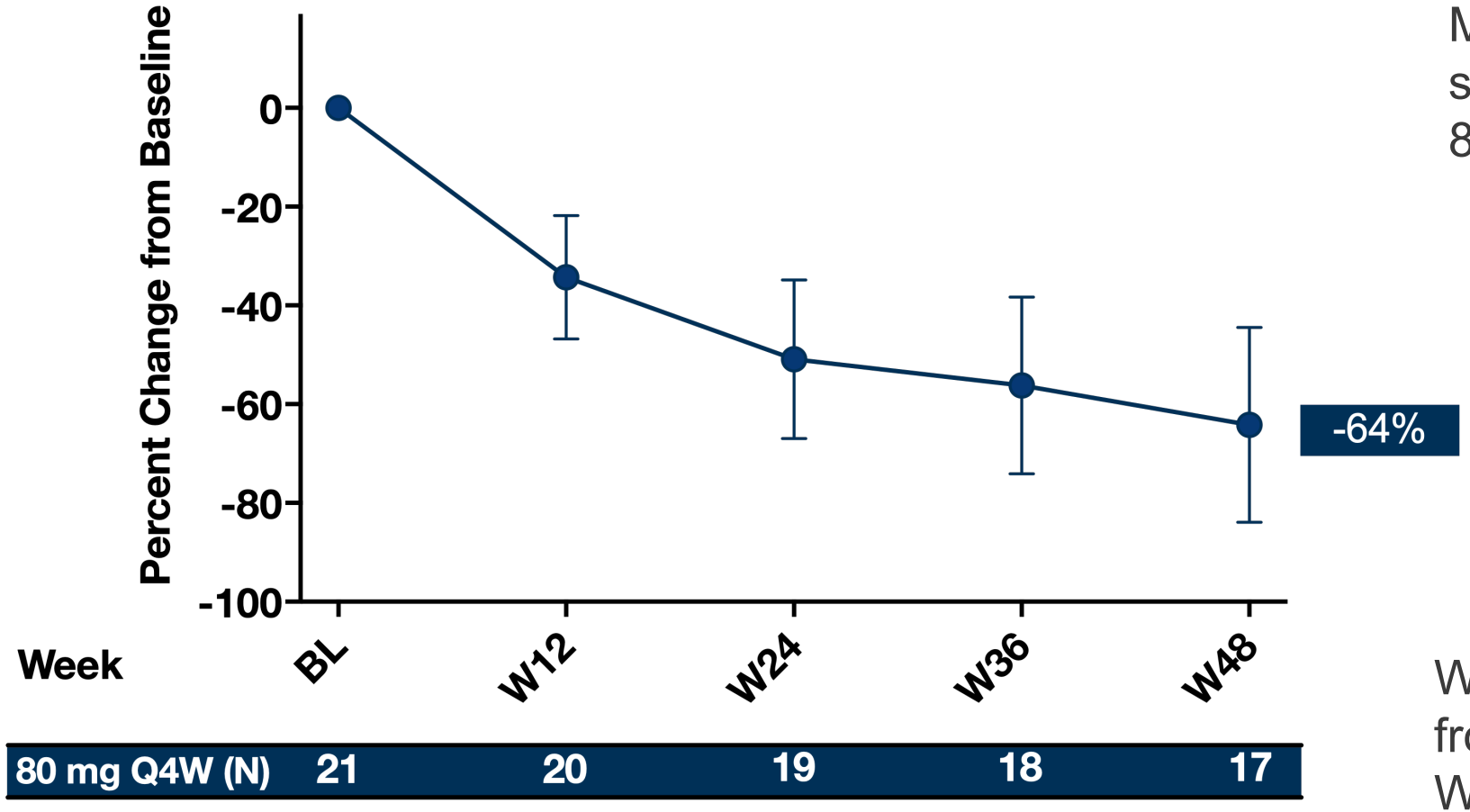
IgAN Baseline Characteristics: Participants With Moderate/Large Hematuria (>50%)

Parameter	Povetacicept 80 mg SC Q4W N = 21	Povetacicept 240 mg SC Q4W N = 33
Age; mean (SD) yr	47.6 (11.7)	45.1 (12.1)
Male; n (%)	7 (33)	18 (55)
Female; n (%)	14 (67)	15 (45)
Race (Asian/White/Other); n (%)	10 (48)/10 (48)/1 (5)	18 (55)/14 (42)/1 (3)
Time since diagnosis; median (min, max) yr	2.1 (0.2, 23.3)	4.0 (0.2, 18.7)
Time since biopsy; mean (SD) yr	2.3 (2.7)	3.0 (3.0)
ACEi/ARB use; n (%)	18 (86)	33 (100)
SGLT2i use; n (%)	6 (29)	15 (45)
Prior immunosuppression use; n (%)	4 (19)	5 (15)
Gd-IgA1; mean (SD) ng/mL	9068 (4324)	7251 (3606)
24-hr UPCR; mean (SD) g/g	1.3 (0.7)	1.2 (0.8)
eGFR; mean (SD) mL/min/1.73 m^2	76.9 (34.0)	63.5 (29.5)
Hematuria moderate or large; n (%)	11 (52)	19 (58)

Note: date of data cut is 13 June 2025

IgAN: Povetacicept Reduced Proteinuria 64% at Week 48

Percent Change from Baseline to Week 48 (Mean ± SE) in 24-hour UPCR – 80 mg Q4W



Mean 24-hour UPCR decreased substantially at 48 weeks with 80 mg Q4W:

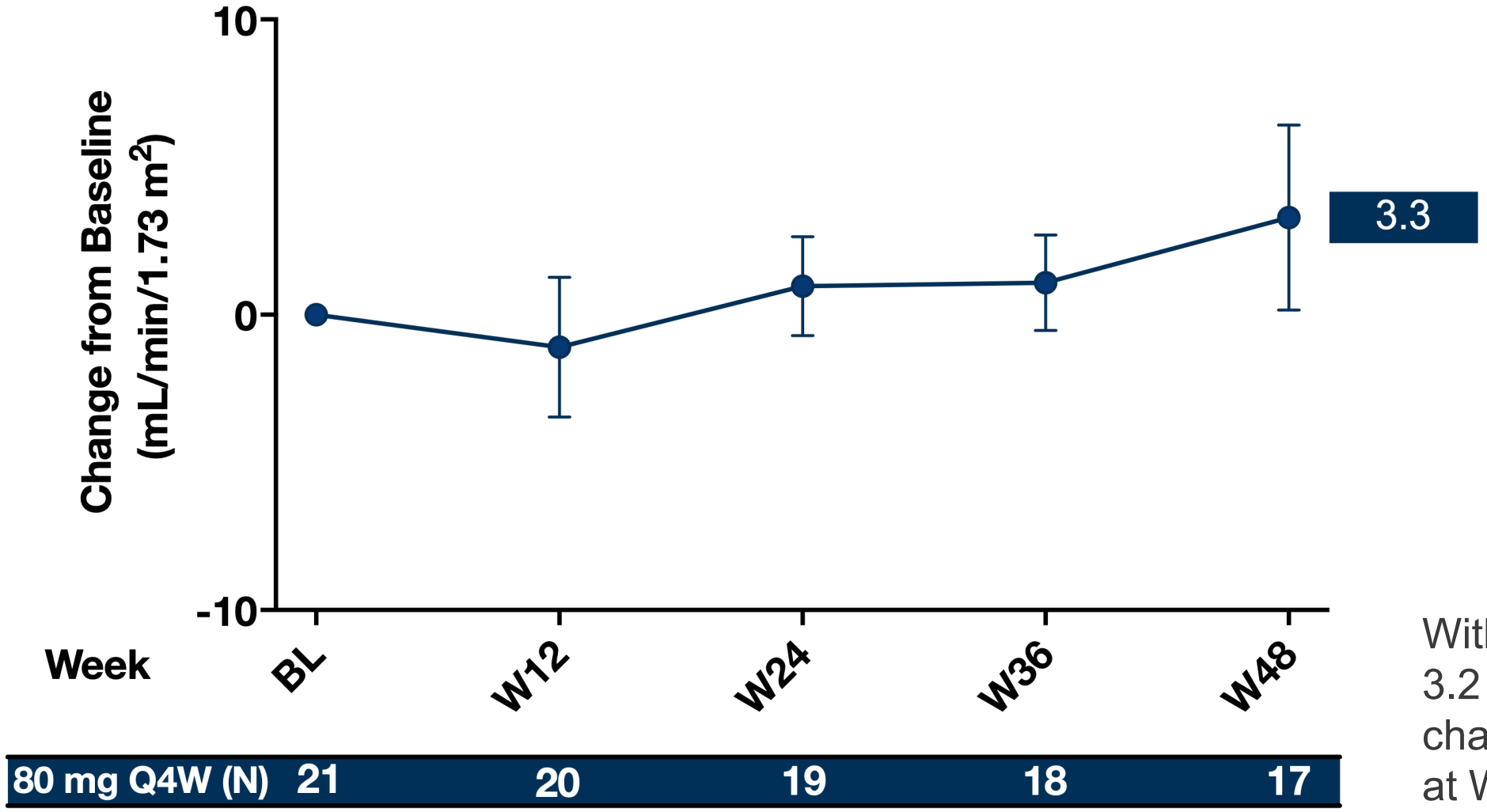
- **64% decrease** from baseline (1.3 g/g to 0.5 g/g)
- **~2/3** participants achieved UPCR <0.5 g/g

With 240 mg Q4W: 56% decrease from baseline (1.2 g/g to 0.6 g/g) at Week 48

Note: date of data cut is 13 June 2025

IgAN: Povetacicept Stabilized eGFR Through Week 48

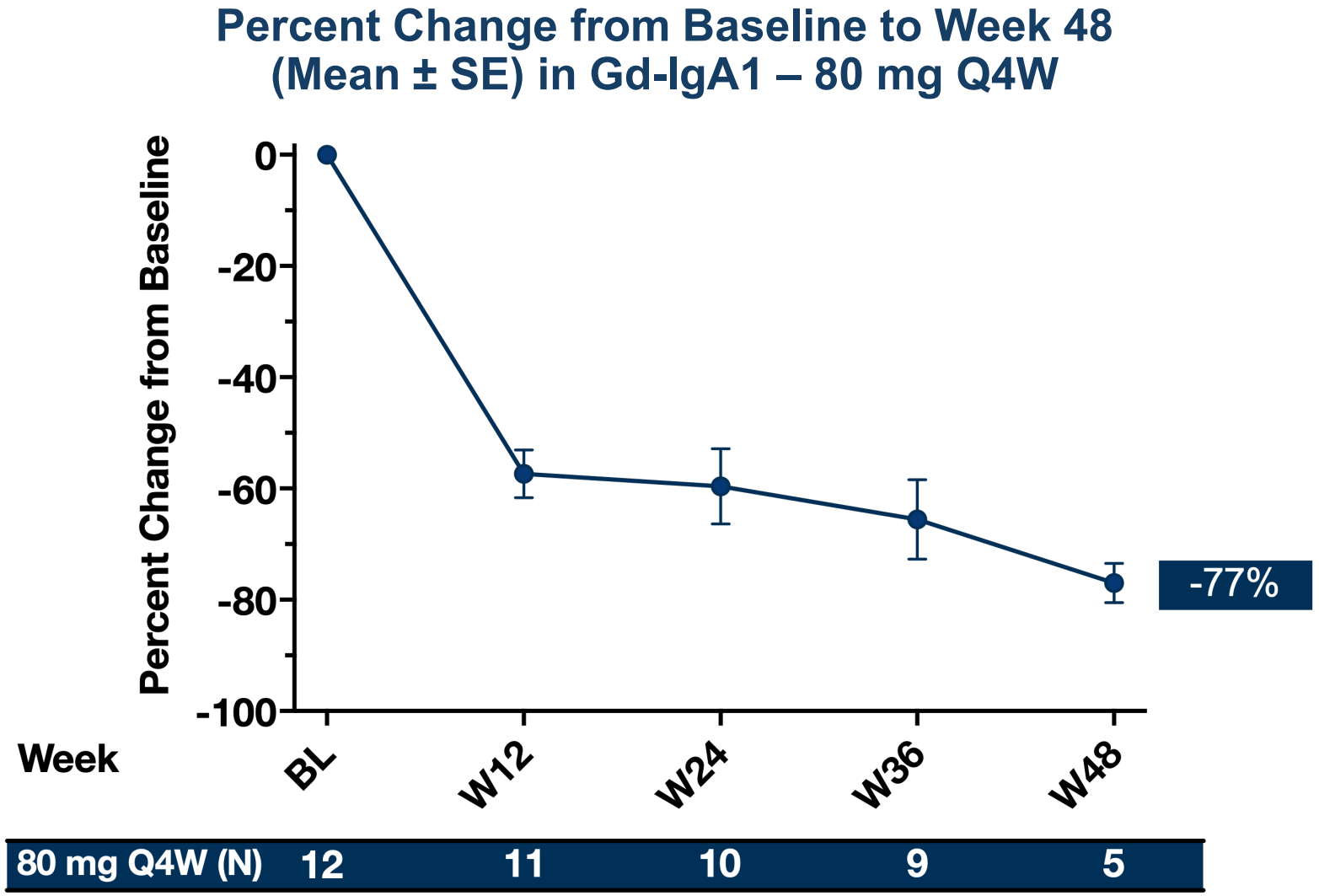
Change from Baseline to Week 48 (Mean ± SE) in eGFR – 80 mg Q4W



With 240 mg Q4W:
3.2 mL/min/1.73 m^2 change from baseline at Week 48

Note: date of data cut is 13 June 2025

IgAN: Early Gd-IgA1 Reduction at Week 12 Continued at Week 48 (77%)



Mean Gd-IgA1 decreased substantially with 80 mg Q4W:

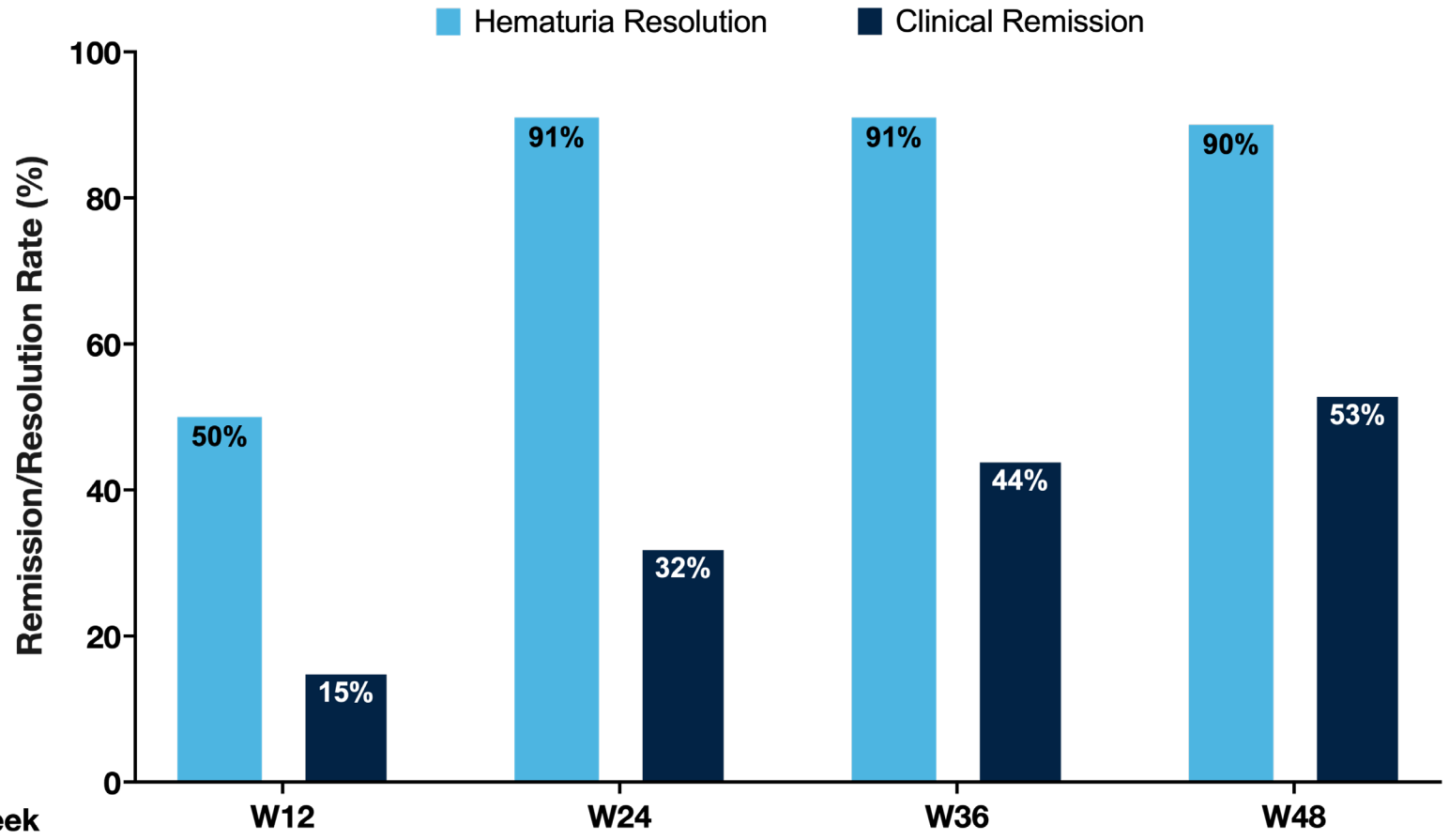
- **Declined early** by **57% at Week 12**
- Reduction **continued at Week 48 by 77%**

With 240 mg Q4W: 77% decrease from baseline at Week 48

Note: date of data cut is 13 June 2025

IgAN: Substantial Proportion of Participants on Povetacicept Achieved Hematuria Resolution (90%) and Clinical Remission (53%)

Clinical Hematuria Resolution and Clinical Remission from Week 12 to Week 48 – 80 mg Q4W



Hematuria Resolution (N)	5/10	10/11	10/11	9/10
Clinical Remission (N)	3/20	6/19	8/18	9/17

Note: Clinical remission is defined as UPCR <0.5 g/g, negative hematuria, and <25% reduction in eGFR versus baseline. Hematuria resolution is defined as a decrease to negative or small levels of urine blood in subjects with baseline urine blood of moderate or large

With 240 mg Q4W:

94% achieved hematuria resolution at Week 48

34% achieved clinical remission at Week 48

Note: date of data cut is 13 June 2025

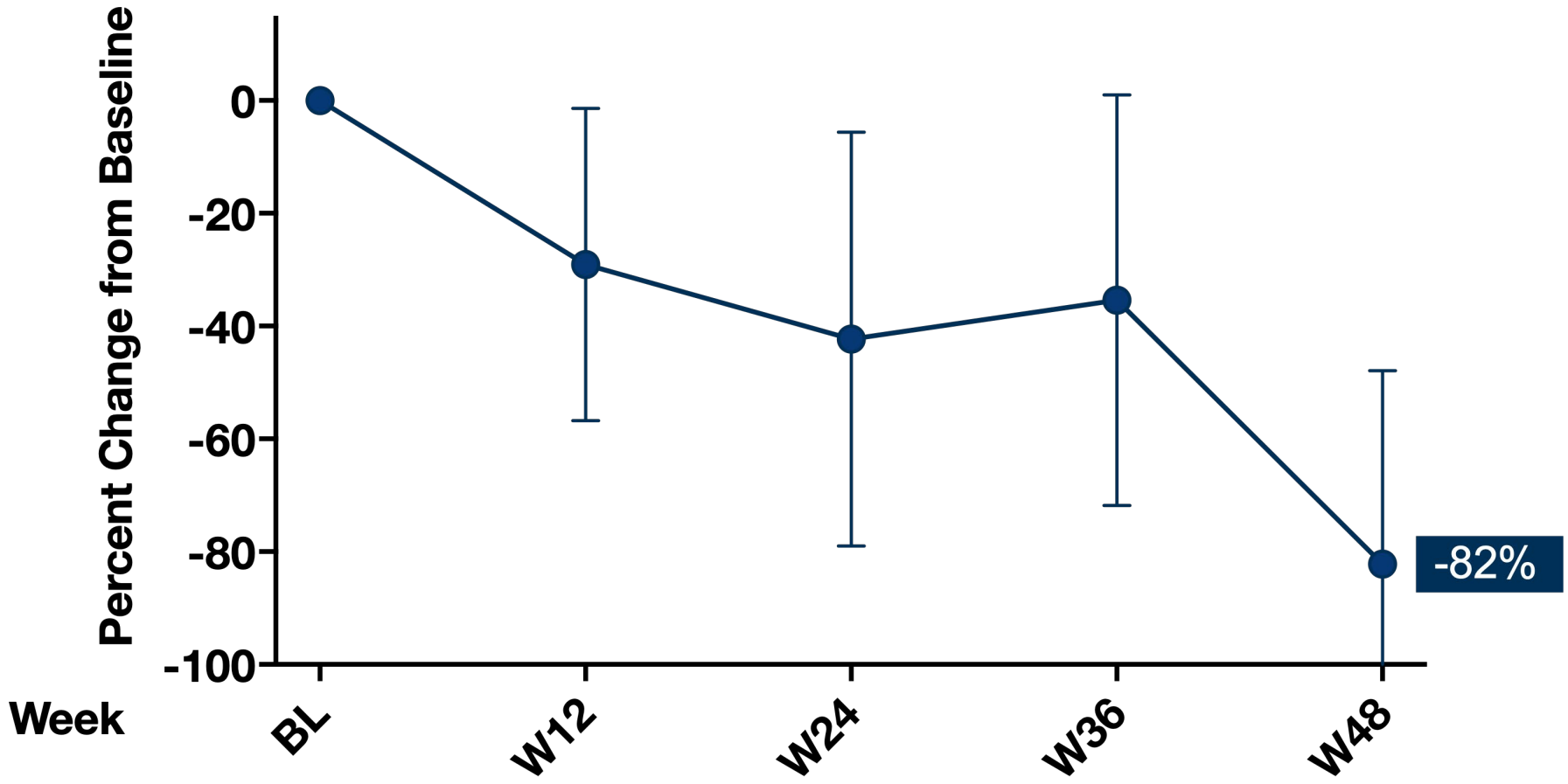
pMN Baseline Characteristics: Participants Had Nephrotic Range Proteinuria (60%) and High Anti-PLA2R Autoantibody Titer

Parameter	Povetacicept 80 mg SC Q4W N = 10
Age; mean (SD) yr	58.2 (18.1)
Male; n (%)	8 (80)
Female; n (%)	2 (20)
Race (Black or African American/White/Asian); n (%)	4 (40)/4 (40)/2 (20)
Time since diagnosis; median (min, max) yr	1.3 (0.3, 9.0)
Time since biopsy; mean (SD) yr	1.7 (2.4)
ACEi/ARB use; n (%)	10 (100)
SGLT2i use; n (%)	3 (30)
Prior immunosuppression use; n (%)	1 (10)
Anti-PLA2R autoantibody; mean (SD) RU/mL	139.5 (92.1)
24-hr UPCR; mean (SD) g/g	3.8 (1.9)
UPCR ≥3.5 g/g (nephrotic range); n (%)	6 (60)
eGFR; mean (SD) mL/min/1.73 m^2	78.1 (24.9)

Note: date of data cut is 13 June 2025

pMN: Povetacicept Reduced Proteinuria 82% at Week 48

Percent Change from Baseline to Week 48 (Mean ± SE) in 24-hour UPCR – All Participants with pMN

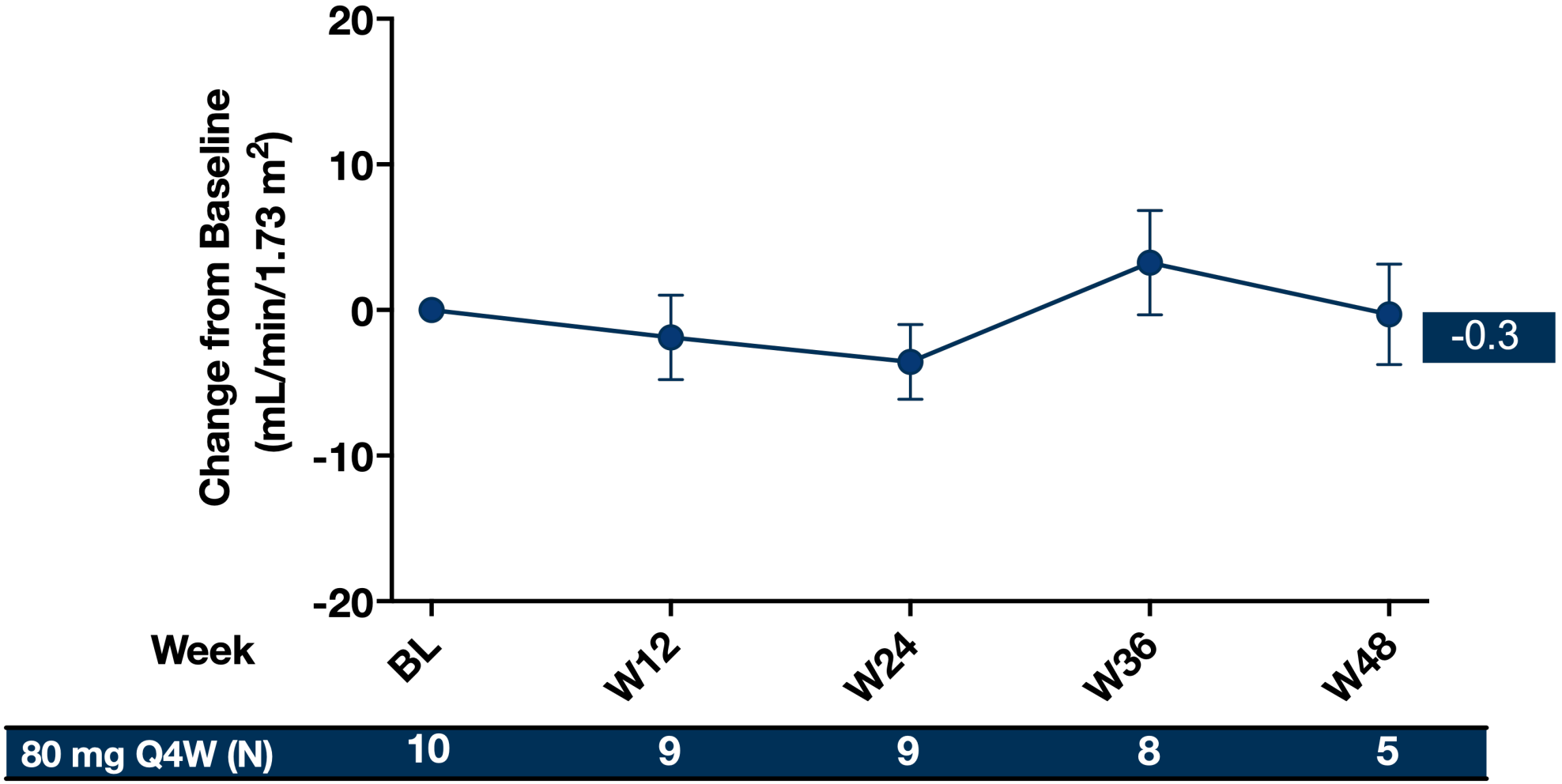


80 mg Q4W (N)	10	9	9	8	5

Note: date of data cut is 13 June 2025

pMN: Povetacicept Stabilized eGFR through Week 48

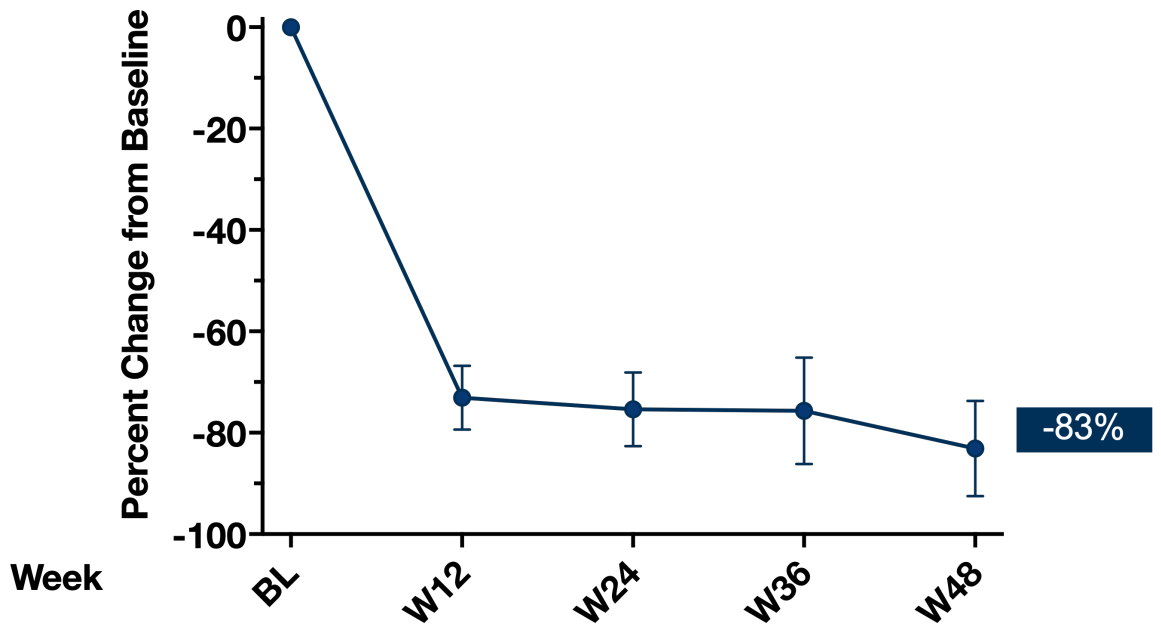
Change from Baseline to Week 48 (Mean ± SE) in eGFR – All Participants with pMN



Note: date of data cut is 13 June 2025

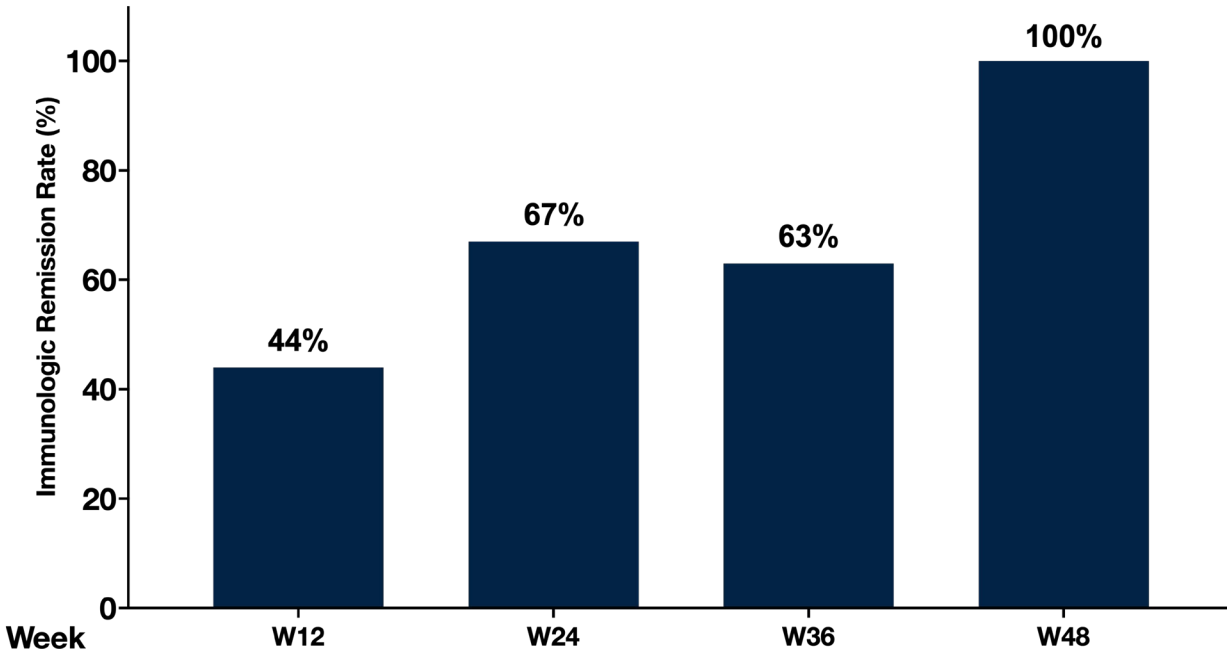
pMN: Povetacicept Reduced Anti-PLA2R Autoantibody 83% Leading to Immunologic Remission in All Participants at Week 48

Percent Change from Baseline to Week 48 (Mean ± SE) in Anti-PLA2R Autoantibody – All Participants with pMN



80 mg Q4W (N)	10	9	9	8	4

Immunologic Remission from Week 12 to Week 48 – All Participants with pMN



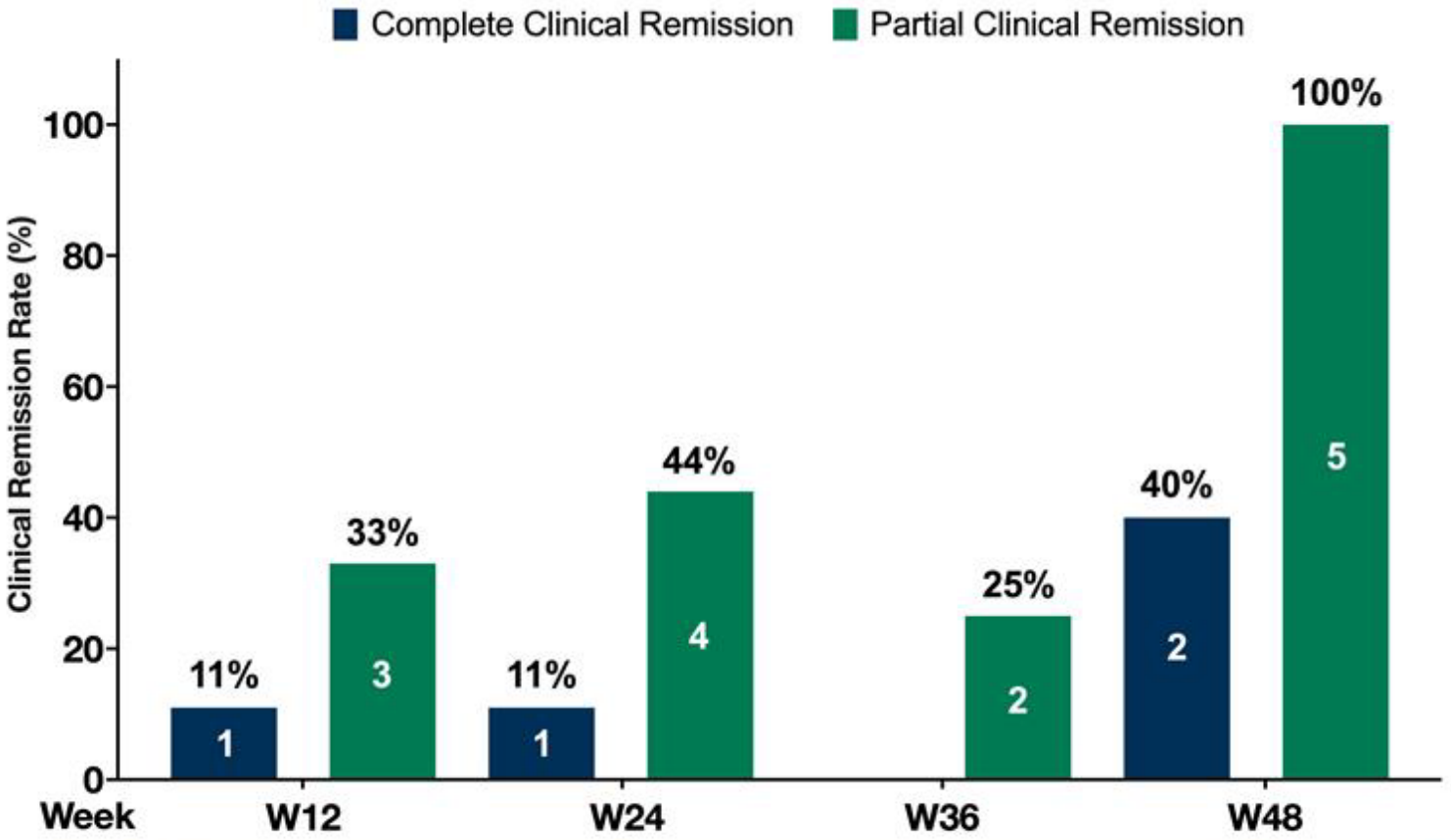
80 mg Q4W (N)	4/9	6/9	5/8	4/4

Note: Immunologic remission is defined as anti-PLA2R autoantibody <14 RU/mL.

Note: date of data cut is 13 June 2025

pMN: All Participants on Povetacicept Achieved Partial Remission and 40% Achieved Complete Clinical Remission at Week 48

Complete and Partial Clinical Remission from Week 12 to Week 48 – All Participants with pMN



	W12	W24	W36	W48
CR (N)	1/9	1/9	0/8	2/5
PR (N)	3/9	4/9	2/8	5/5

Note: Complete clinical remission is defined as UPCR <0.5 g/g. Partial clinical remission is defined as UPCR <3.5 g/g and >50% reduction from baseline. .

Note: date of data cut is 13 June 2025

Povetacicept Was Generally Safe and Well Tolerated in Both IgAN and pMN

Parameter	IgAN Povetacicept 80mg SC Q4W N = 21	IgAN Povetacicept 240mg SC Q4W N = 33	pMN Povetacicept 80mg SC Q4W N = 10
Any AE; n (%)	16 (76)	27 (82)	8 (80)
Grade 1/mild	6 (29)	7 (21)	4 (40)
Grade 2/moderate	9 (43)	19 (58)	2 (20)
Grade 3/severe	1 (5)[a]	1 (3)[b]	2 (20)[c, d]
Grade ≥4/life-threatening, death	0	0	0
Related AEs; n (%)	6 (29)	10 (30)	3 (30)
AEs leading to discontinuation; n (%)	0	1 (3)[b]	2 (20)[c, d]
SAE; n (%)	1 (5)[e]	1 (3)[b]	1 (10)[c]
Severe hypogammaglobulinemia; n (%) **(IgAN: IgG <300 mg/dL; pMN: <150 mg/dL)**	1 (5)	4 (12)	1 (10)[d]
Malignancy; n (%)	1 (5)[a]	0	0
Any infection; n (%)	9 (43)	21 (64)	2 (20)
Grade 3/severe	0	1 (3)[b]	1 (10)[c]
Administration-related reaction or injection site reaction; n (%)	3 (14)	4 (12)	2 (20)

Notes: Includes up to 104 weeks of data.
[a] Grade 3 event of carcinoma was not related to povetacicept.
[b] Grade 3 event of urinary tract infection was not related to povetacicept; participant discontinued per protocol.
[c] Grade 3 event of pneumonia was not related to povetacicept; treatment was withdrawn per protocol.
[d] Grade 3 non-serious event of hypogammaglobulinemia was related to povetacicept; treatment was withdrawn per protocol.
[e] Grade 1 event of dermatitis was not related to povetacicept; resolved following treatment.

Note: date of data cut is 13 June 2025

- Most AEs were **mild to moderate in severity**
- **No SAEs related** to povetacicept
- **No safety concerns** observed with laboratory parameters
- **No clinically meaningful trends** in ECGs or vital signs

Conclusions

- Povetacicept 80 mg Q4W led to early, substantial, and sustained improvements in IgAN
  - **Proteinuria declined 64%** at Week 48
  - **eGFR** was **stable** through Week 48
  - **Gd-IgA1 declined early by 57%** at Week 12 and continued at Week 48 with a **77% decline**
  - **Hematuria resolution** was **achieved** by **90%** of participants with medium/large hematuria at baseline
  - **Clinical remission** was **achieved** by **53%** of participants by Week 48.
- Similar results were seen in **pMN** with **substantial declines in proteinuria and anti-PLA2R autoantibody, stable eGFR, 100% immunologic remission, and 100% complete or partial clinical remission** at Week 48.
- Povetacicept was generally **safe and well tolerated.**
- Results **support the ongoing, fully enrolled Phase 3 RAINIER study** of Povetacicept in IgAN and **ongoing Phase 2b/3 OLYMPUS study** of Povetacicept in pMN.

Data Highlight the Potential for Povetacicept to be a Best-in-class, Transformative, Disease-modifying Treatment for IgAN and pMN

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Sug Kyun Shin	Ilsan Hospital
Sung Gyun Kim	Hallym University Sacred Heart Hospital
Yong Kyu Lee	Ilsan Hospital

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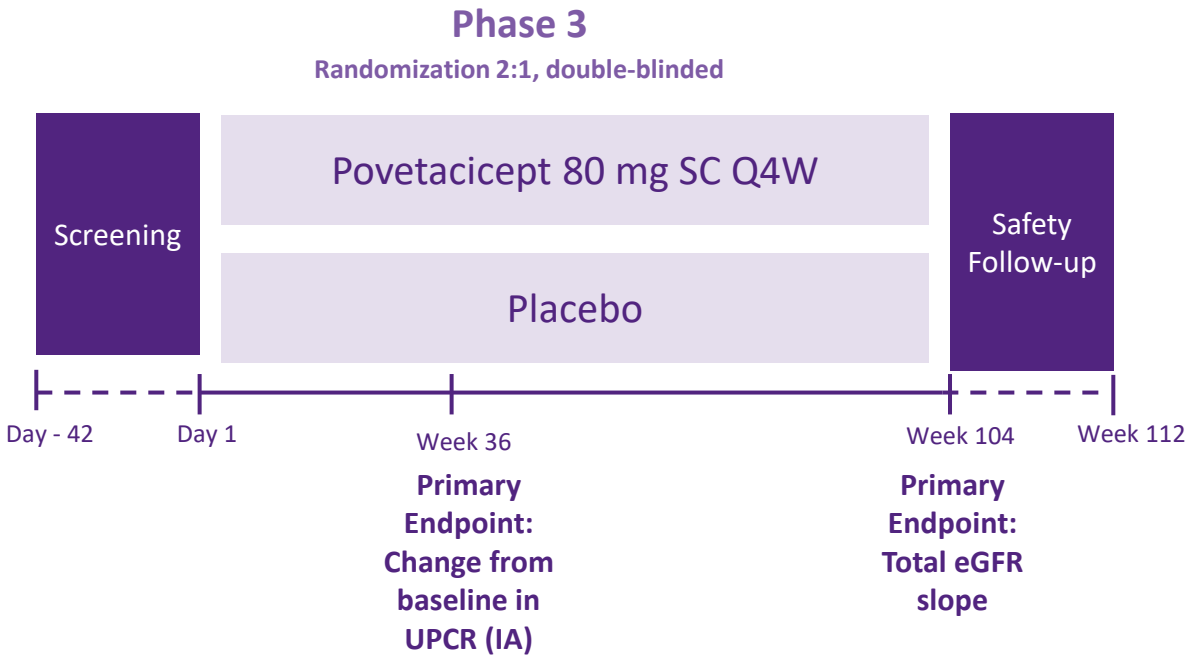
***Areas of Expertise**: Nephrology, glomerular disease, amyloidosis, kidney and pancreas transplantation, pathogenesis of IgA nephritis*

- RAINIER pivotal study

Disclosures: Dr. Lafayette has received research support from NIH, UPenn, UMich, Beigene, Biogen, Calliditas, Travere, Vera, Roche, Alexion, Otsuka and is a consultant for Vertex Pharmaceuticals, Amgen, Alexion, Biogen, Calliditas, Otsuka, Travere, Takeda and Vera.

RAINIER pivotal trial for povetacicept in IgAN is fully enrolled

~15 months to complete full enrollment of ~600 patients



Population:

- Adults with IgAN (biopsy-verified)
- 24-hour proteinuria excretion ≥1 g/day or 24-hour uPCR ≥0.75 g/g
- eGFR ≥30 mL/min/1.73 m^2
- Stable doses of ACEi/ARB therapy
- Stable doses of SGLT2 inhibitors, MRAs and ETAs allowed

Primary Endpoint:

- Change from baseline in 24-hour UPCR at Week 36 and the total eGFR slope through Week 104

Secondary endpoints:

- Change from baseline in serum Gd-IgA1 at Week 36
- Proportion of subjects to achieve hematuria resolution at Week 36 (among subjects with hematuria at baseline)
- Change from baseline in eGFR at Week 104
- Time to kidney disease progression, defined as ≥30% decline in eGFR, ESKD, or non-accidental death through Week 104

Povetacicept is an investigational product that has not been approved by any health authority. The safety and effectiveness of povetacicept have not been established.

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; Q4W, every 4 weeks; SC, subcutaneous; uPCR, urine protein creatinine ratio. FACIT-Fatigue Score, functional assessment of chronic illness therapy – fatigue score; Q4W, every 4 weeks; SC, subcutaneous; uPCR, urine protein creatinine ratio; IA, interim analysis.

Brad Rovin, M.D.

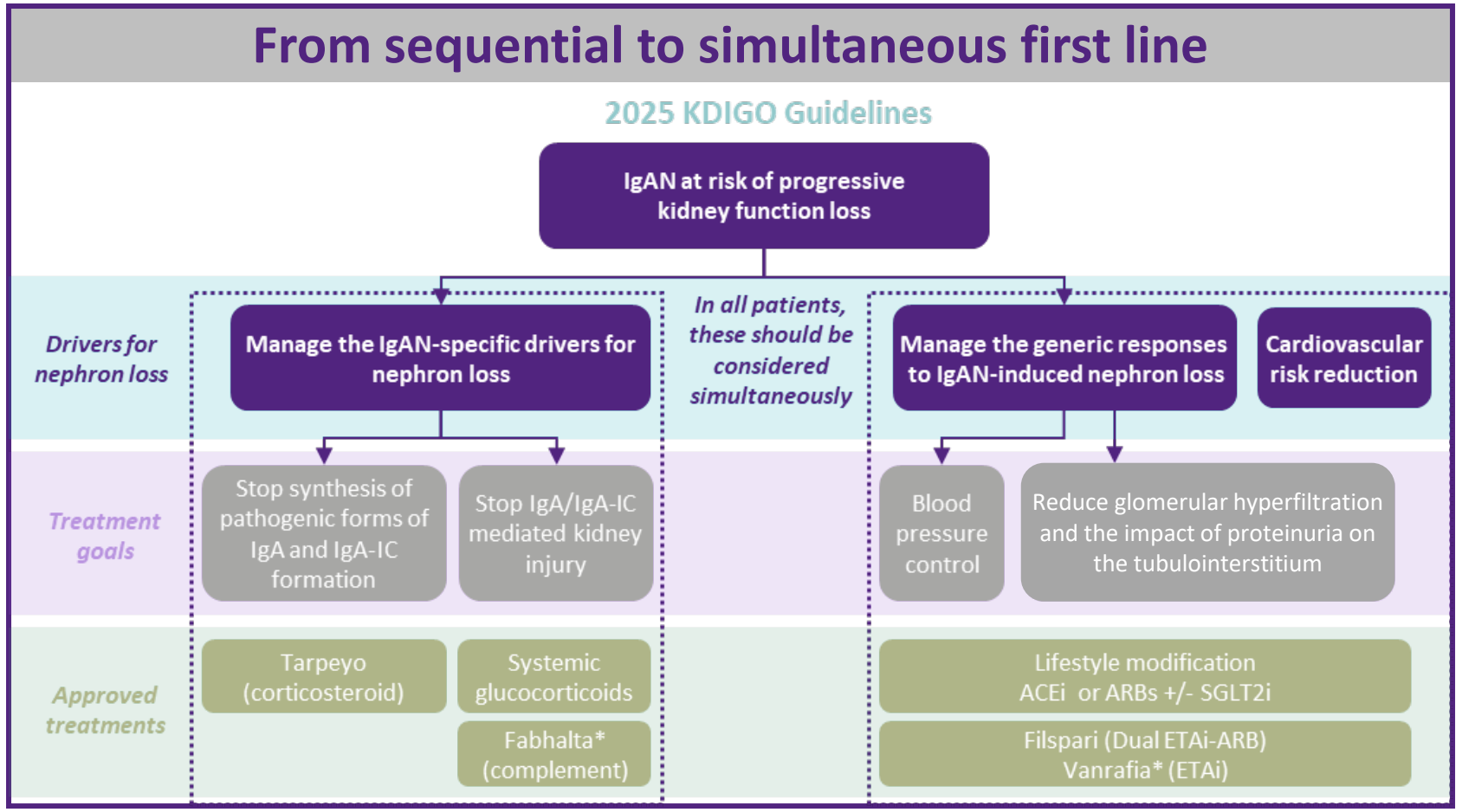
Director, Division of Nephrology, Vice Chair of Research, Professor of Internal Medicine, Ohio State University Wexner Medical Center

***Areas of Expertise**: Nephrology, glomerulonephritis, kidney disease*

- Evolving standard of care in IgAN
- Role of guidelines in the treatment of IgAN

Disclosures: Dr. Rovin has received research support from the LRA, NIH, Biogen and is a consultant for Vertex Pharmaceuticals, Genentech, Biogen, Aurinia, Alexion, Astra-Zeneca, BMS, BI, Vera, Calliditas, Century, Regeneron and Novartis

Treatment of IgAN now recommends shift from sequential to simultaneous + early and more aggressive intervention, with a redefined proteinuria threshold for “high-risk”

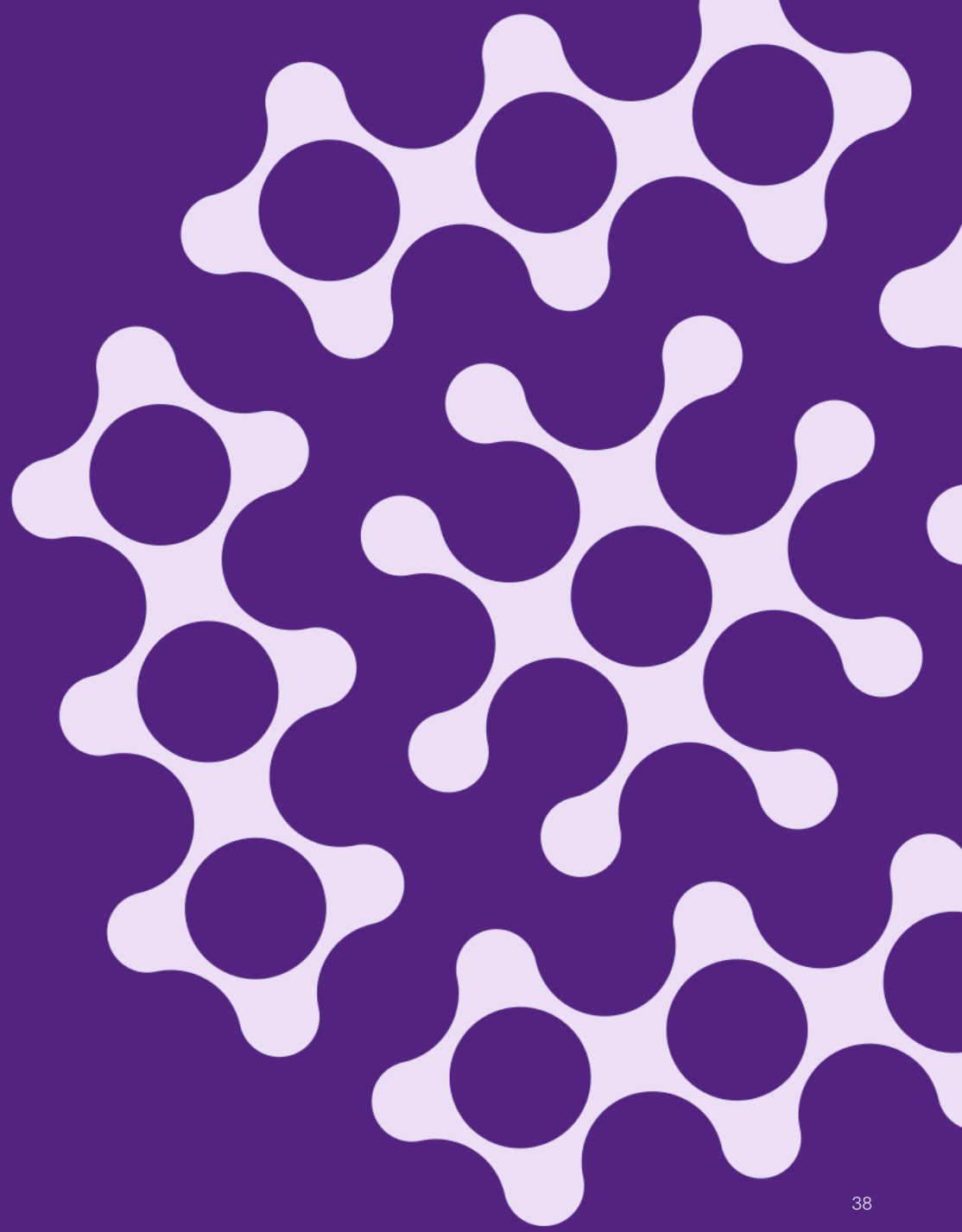


Sources: Patient Chart Dynamix (2025); 2025 KDIGO Guidelines

Notes: IgAN = Immunoglobin A nephropathy, ACE = angiotensin-converting enzyme inhibitors, ARB = angiotensin receptor blocker, SGLT2i = sodium-glucose cotransporter 2 inhibitor, CKD = chronic kidney disease, ETAi = endothelin receptor A antagonist, UPCR = urine protein-to-creatinine ratio

Q&A Session

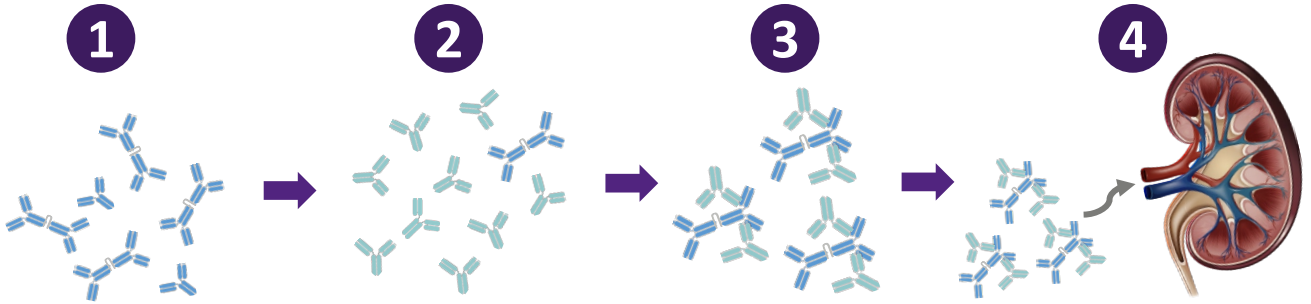
Appendix: Disease area backgrounders



IgAN: A serious autoimmune disease due to uncontrolled B cell activity; most patients are at risk of kidney failure within their lifetimes

- IgAN is a global disease with **>300k diagnosed patients** in U.S. and Europe[1] (>1M patients globally)
- Up to ~72% of adults with IgAN progress to kidney failure or death within 20 years of diagnosis
- Significant unmet need for advanced disease-modifying therapies targeting the causal biology of disease

The 4-hit hypothesis



Pathogenic IgA immune complexes accumulate in the kidney glomeruli, provoking complement activation, inflammation and glomerular injury

BAFF

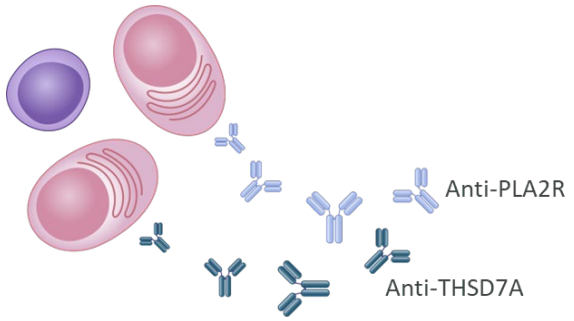
APRIL

eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; IgAN, immunoglobulin A nephropathy; UPCR, urine protein creatinine ratio. Figures reproduced from Pitcher D et al. Clin J Am Soc Nephrol. 2023;18(6):727–728. ***References: 1.*** *Suzuki H, et al. J Clin Med. 2024;13(15):4495.*

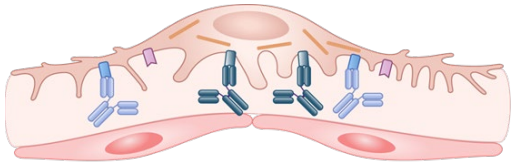
pMN: A rare, autoimmune disease caused by pathogenic antibodies that target kidney podocytes, leading to long-term kidney damage

- ~150k individuals diagnosed with pMN in the US and Europe (~500K patients globally)
- Less than 50% of people with pMN achieve complete remission with existing therapies; no approved treatments to date
- ~35–40% of people with pMN with nephrotic range proteinuria may progress to end-stage kidney disease within 10 years
- Significant unmet need for advanced disease-modifying therapies targeting the causal biology of disease

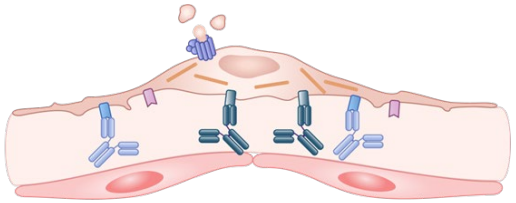
Pathogenesis of pMN



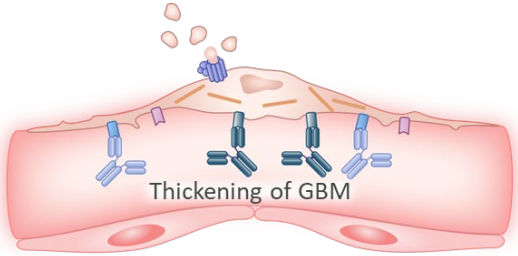
1 Formation of autoantibodies



2 Formation of immune complexes in the glomerulus



3 Activation of complement and podocyte injury



4 Structural changes to the glomerulus

pMN, primary membranous nephropathy; PLA2R, Phospholipase A2 Receptor.

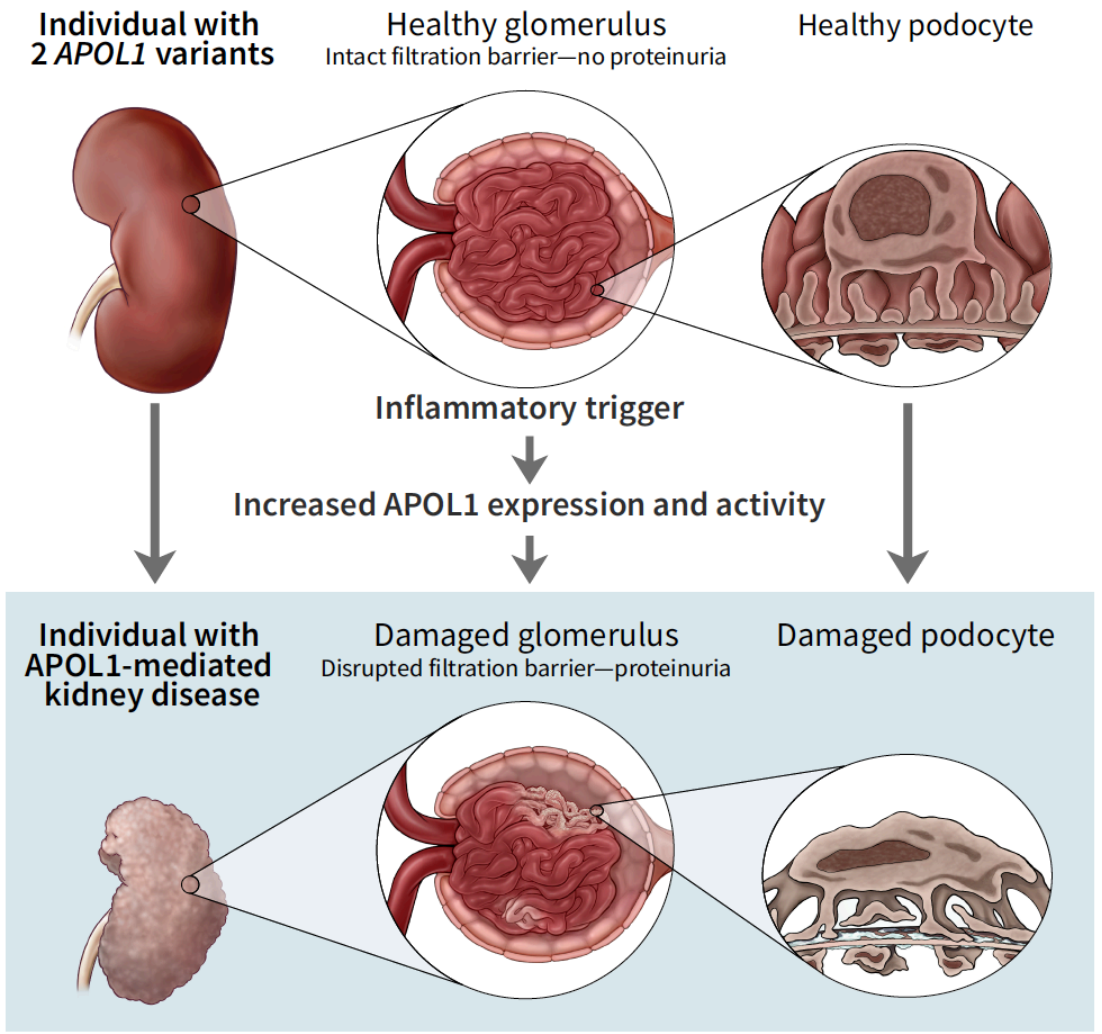
AMKD: toxic gain-of-function APOL1 variants lead to proteinuria, kidney function decline and kidney failure

- **~250,000** people in the U.S. & Europe living with AMKD, majority not diagnosed; occurs in people of African ancestry

- AMKD is a genetic, rapidly progressive, proteinuric kidney disease
- 2 APOL1 risk variants lead to toxic gain-of-function damage resulting in podocytopathy and proteinuria

- No approved treatments for AMKD; currently available treatments do not address the underlying cause of disease
- Median age of kidney failure: 45 years

AMKD causal human biology



Egbuna, Ogo & Audard, Vincent & Manos, George & Tian, Simon & Hagos, Fanuel & Chertow, Glenn. (2024). Safety and Tolerability of the APOL1 Inhibitor, Inaxaplin, Following Single- and Multiple-ascending Doses in Healthy Adults. Glomerular Diseases. 4. 10.1159/000538255.

ADPKD: Kidney cysts lead to kidney function decline and kidney failure

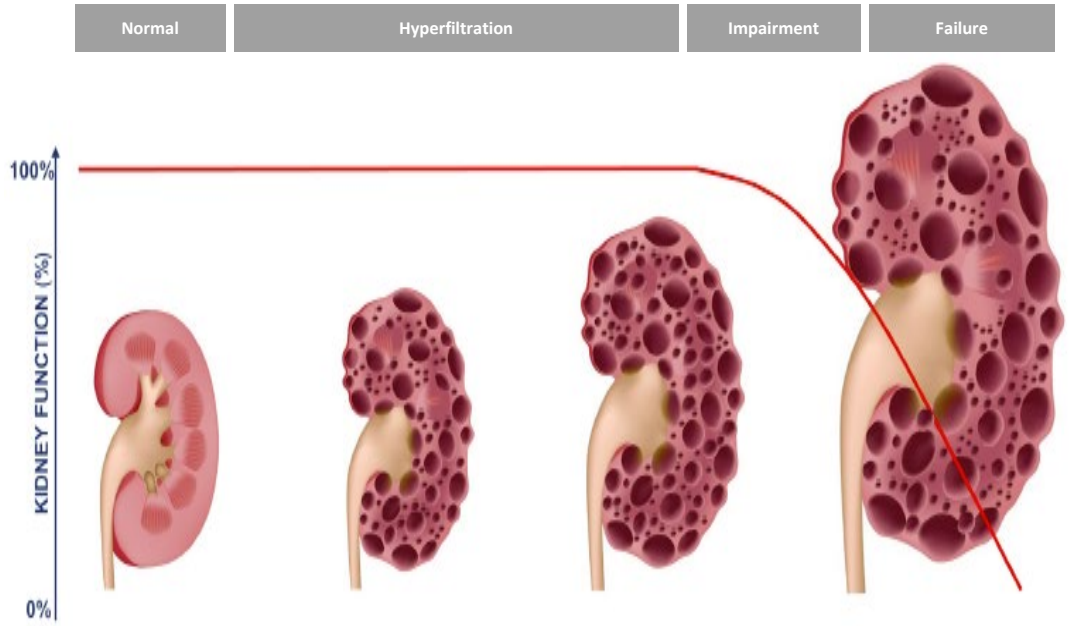
- **~300,000** people in the U.S. & Europe diagnosed with ADPKD

- Most common genetic cause of kidney failure (5-10%)
- Vast majority of variants are in the *PKD1* gene, leading to defects in the PC1 protein

- No treatments currently available to address the underlying cause of disease
- Median age of kidney failure: 60 years

ADPKD: autosomal dominant polycystic kidney disease; HV: healthy volunteers.

Over time, kidney cysts lead to kidney function (eGFR) decline and kidney failure



Goal: Target the underlying cause of ADPKD by restoring PC1 protein function, thereby reducing total kidney volume and preventing progression to kidney failure