

ORIGIN 3: Subgroup Analysis of a Phase 3 Trial of Atacept in IgA Nephropathy

Jonathan Barratt,¹ Sean Barbour,² Robert Brenner,³ Kirk Campbell,⁴ Necmi Eren,⁵ Jürgen Floege,⁶ Vivekanand Jha,⁷ Dana Rizk,⁸ Hitoshi Suzuki,⁹ Hernan Trimarchi,¹⁰ Hong Zhang,¹¹ Richard Lafayette¹²

¹University of Leicester, Leicester, UK; ²The University of British Columbia, Vancouver, Canada; ³Vera Therapeutics, Inc., Brisbane, CA, USA; ⁴University of Pennsylvania, Philadelphia, PA, USA; ⁵Kocaeli University, Kocaeli, Turkey; ⁶Rheinisch-Westfälische Technische Hochschule Aachen University Hospital, Aachen, Germany; ⁷The George Institute for Global Health, New Delhi, India; ⁸University of Alabama at Birmingham, Birmingham, AL, USA; ⁹Junendo University Urayasu Hospital, Chiba, Japan; ¹⁰Hospital Británico de Buenos Aires, Buenos Aires, Argentina; ¹¹Peking University First Hospital, Beijing, China; ¹²Glomerular Disease Center, Stanford University, Stanford, CA, USA.

INTRODUCTION

IgAN: B-Cell-Mediated Disease With High Unmet Need for Disease-Modifying Therapies

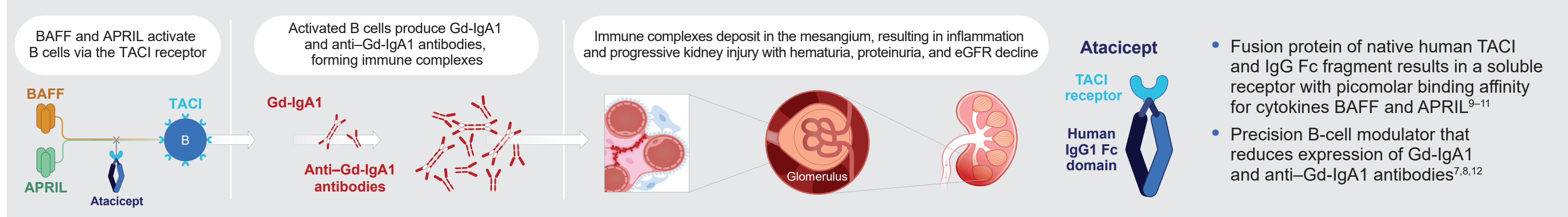
- IgAN is a **B-cell-mediated** immune complex glomerulonephritis associated with four disease markers^{1,2}:



- Supportive-care therapies** (eg, RASi and SGLT2i) reduce proteinuria but **do not address the upstream immunologic drivers of IgAN**³

- Despite supportive care, ≥50% of patients progress to kidney failure or death within 10–20 years of diagnosis^{4,5}
- The current treatment **goal** is to stabilize kidney function by limiting the rate of eGFR loss to <1 mL/min/1.73 m²/year for most adults⁶
- Targeting **B-cell-mediated disease pathways** represents a logical disease-modifying approach aimed at reducing Gd-IgA1 and anti-Gd-IgA1 antibodies

Atacept Is a Rationally Designed Fusion Protein In Late-Stage Clinical Development for the Treatment of IgAN

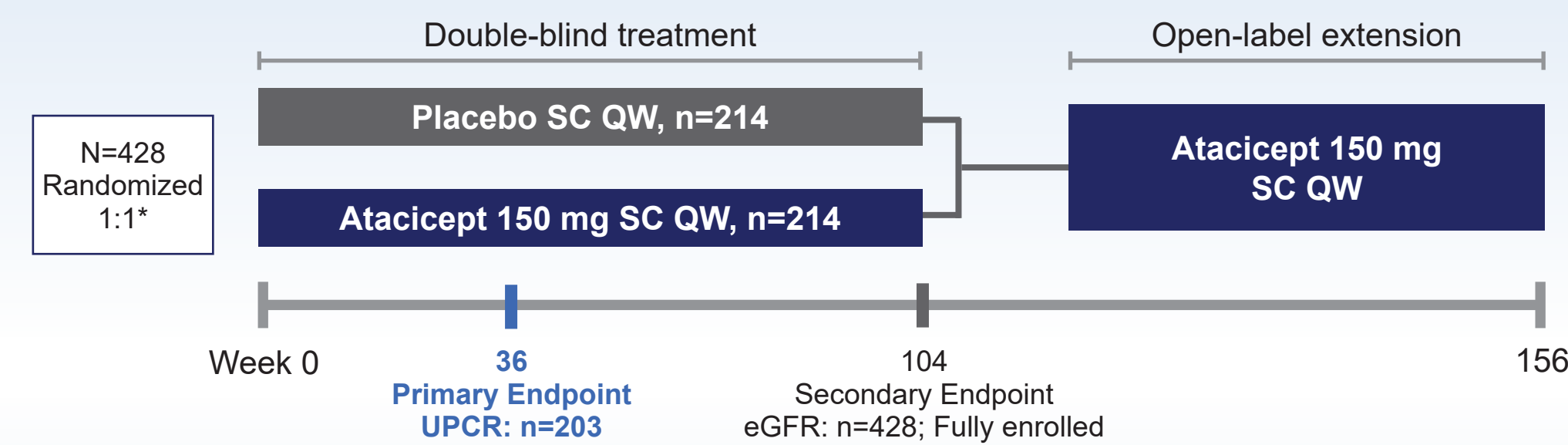


- In the ORIGIN 2b and 3 trials, atacept demonstrated a safety profile that was comparable to placebo^{7,8}

- In the ORIGIN Phase 2b and 3 trials, **atacept consistently reduced proteinuria, Gd-IgA1, and hematuria**^{7,8}; atacept **stabilized eGFR** in the ORIGIN 2b trial⁷

METHODS

ORIGIN3 Trial Design⁸: Global, randomized, placebo-controlled trial of atacept, self-administered at home via weekly 1 mL SC injection



*Stratified by screening eGFR values (<45 mL/min/1.73 m² or ≥45 to <90 mL/min/1.73 m², or ≥90 mL/min/1.73 m²), screening total urine protein excretion (<2 g/24h or ≥2 g/24h), stable SGLT2i use at screening (yes or no) and geographic region (Asia or any other region).

- Ad hoc analyses of ORIGIN 3 were expanded to include
- Race (Asian vs Non-Asian)
 - Participants with proteinuria <1.0 or ≥1.0 g/g
 - eGFR <45 or ≥45 mL/min/1.73 m²
 - Participants with histopathological disease scores (MEST-C)



Scan to view ORIGIN 3 interim analysis manuscript (Lafayette R, et al. *N Engl J Med*. 2026)



Key Inclusion Criteria

- ≥18 years old with biopsy-proven IgAN and high risk of disease progression
- Stable and optimized RASi for ≥12 weeks; use of SGLT2i allowed
- UPCR-24h ≥1.0 g/g or UP ≥1.0 g per 24h
- eGFR ≥30 mL/min/1.73 m²
- Blood pressure ≤150/90 mmHg



Key Endpoints

- Primary efficacy: UPCR-24h % change at Week 36
- Key secondary: eGFR change at Week 104
- Gd-IgA1 change
- Hematuria resolution
- Safety

KEY TAKEAWAYS



Atacept is a native human TACI-Fc fusion protein that inhibits BAFF and APRIL, key drivers of B-cell activity central to IgAN pathophysiology



In ORIGIN 3, atacept reduced proteinuria and Gd-IgA1 levels, with resolution of hematuria, and demonstrated a safety profile comparable with placebo



Proteinuria reduction with atacept was consistent across subgroups, including those with proteinuria <1.0 or ≥1.0 g/g and eGFR <45 or ≥45 mL/min/1.73 m²

SCAN TO
DOWNLOAD



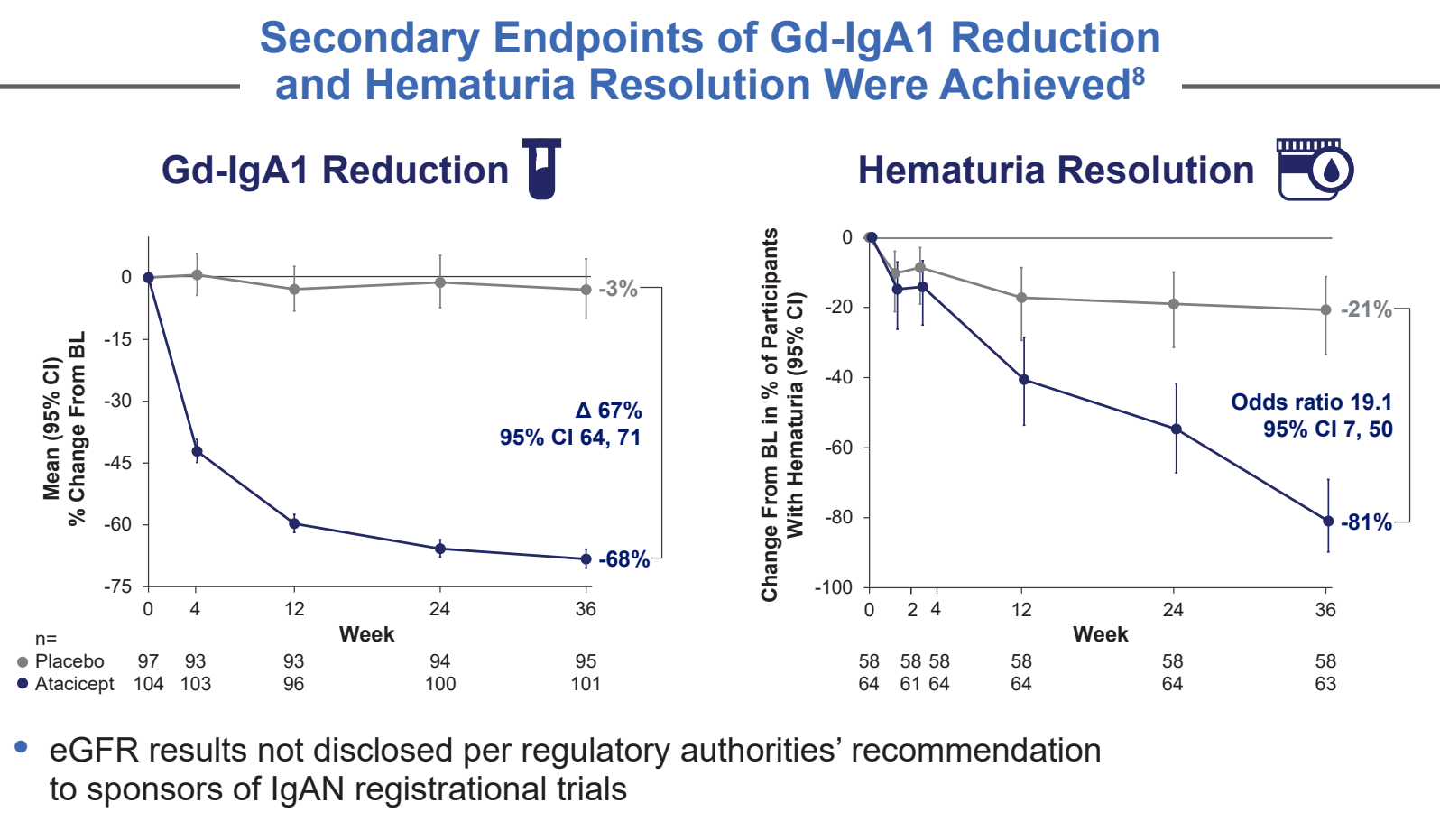
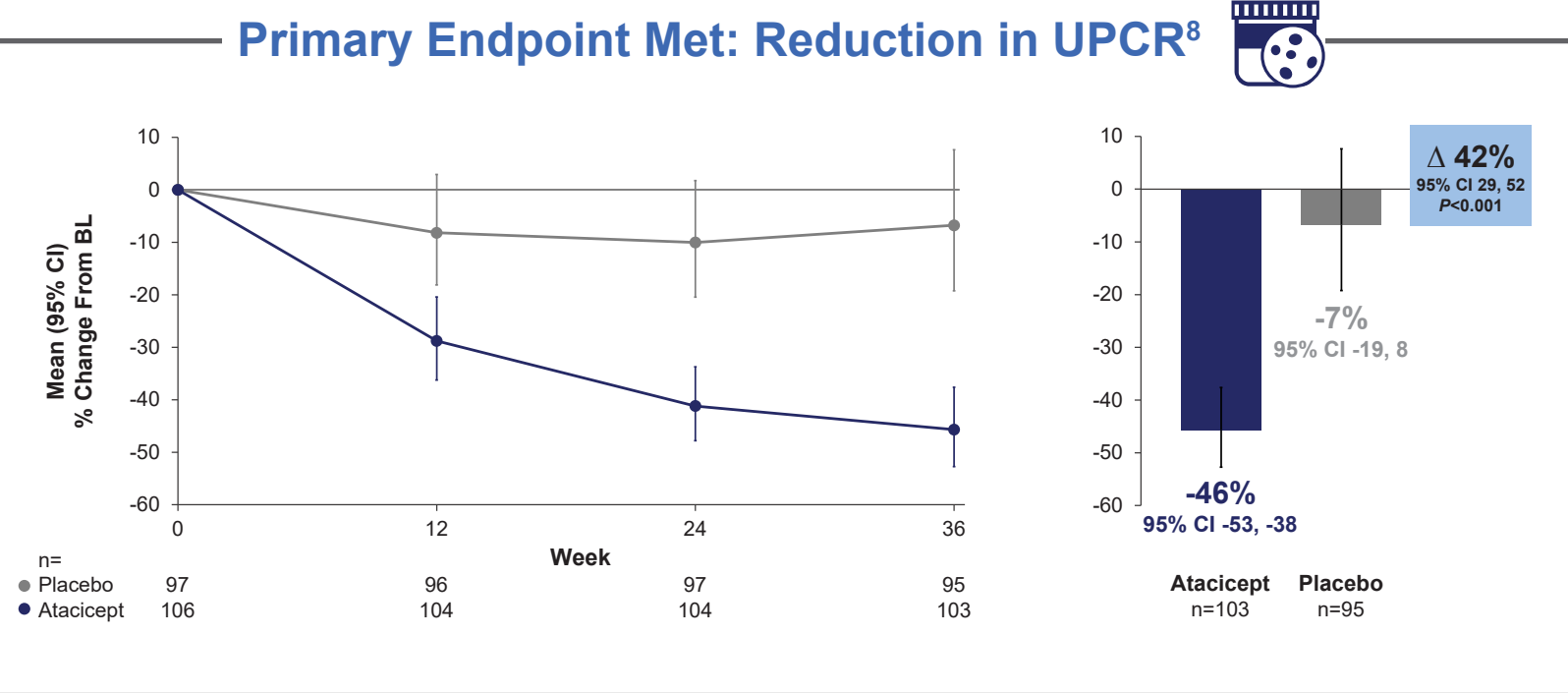
RESULTS

UPCR Efficacy Demonstrated Across All Subgroups^{8,10}

	n (%)		Mean UPCR % Change at Week 36		Favors placebo	Favors atacept	Mean UPCR % Reduction vs Placebo (95% CI)
	Atacept	Placebo	Atacept	Placebo			
Overall	106	97	-46%	-7%			42% (29, 52)
Age, years	<40	48 (45)	49 (51)	-44%	+0.5%		45% (23, 60)
	≥40	58 (55)	48 (49)	-46%	-14%		38% (21, 51)
Sex	Male	57 (54)	58 (60)	-41%	-9%		35% (14, 51)
	Female	49 (46)	39 (40)	-51%	-2%		50% (34, 62)
Region	Asia	50 (47)	48 (49)	-50%	-14%		42% (18, 58)
	Other	56 (53)	49 (51)	-42%	+1%		43% (29, 55)
Race	White	46 (43)	42 (43)	-42%	+0.1%		42% (26, 55)
	Non-White	60 (57)	55 (57)	-48%	-11%		42% (22, 57)
BL UPCR, g/g	Asian	59 (56)	52 (54)	-47%	-12%		40% (19, 56)
	Non-Asian	47 (44)	45 (36)	-44%	+1%		45% (29, 56)
BL eGFR, mL/min/1.73 m ²	<1.5	53 (50)	47 (48)	-44%	+3%		46% (28, 59)
	≥1.5	53 (50)	50 (52)	-48%	-13%		41% (21, 55)
BL eGFR, mL/min/1.73 m ²	<1.0	25 (24)	29 (3)	-42%	+5%		45% (17, 64)
	≥1.0	81 (76)	68 (70)	-48%	-10%		42% (27, 54)
SGLT2i use at BL	<60	50 (47)	52 (54)	-35%	-1%		34% (13, 51)
	≥60	56 (53)	45 (46)	-53%	-14%		45% (27, 59)
SGLT2i use at BL	<45	33 (31)	34 (35)	-38%	+3%		40% (15, 58)
	≥45	73 (69)	63 (65)	-49%	-11%		43% (26, 55)
SGLT2i use at BL	Yes	59 (56)	49 (51)	-48%	-7%		44% (26, 58)
	No	47 (44)	48 (49)	-43%	-6%		39% (19, 54)

Blue boxes denote expanded ad hoc analyses.
Subgroup analyses are exploratory and not adjusted for multiplicity.

- Mean time from biopsy to enrollment was approximately 2.5 years
- Consistent treatment effect of atacept was observed across all MEST-C subgroups



AEs Were Generally Balanced Between Groups ⁸		
Participants, n (%)	Atacept (n=214)	Placebo (n=214)
AEs	127 (59)	107 (50)
Serious AEs	1 (0.5)	11 (5)
AEs leading to drug discontinuation	2 (1)	8 (4)
AEs of infections and infestations	68 (32)	60 (28)
Serious or severe infections and infestations	0	3 (1)
Opportunistic infections	0	0
Study-drug-related AEs	63 (29)	22 (10)
AEs associated with ISRs	51 (24)	11 (5)
Hypersensitivity reactions	8 (4)	14 (7)
AEs leading to death	0	0

Analysis of the safety population (all participants randomized and treated, n=428) as of interim data cut on May 15, 2025.

- Most AEs were mild or moderate in severity
- The rate of serious AEs was lower in the atacept group compared with placebo
- No deaths occurred in either group
- No observed hypogammaglobulinemia (IgG <3 g/dL)

PIONEER: A Basket Trial of Atacicept in Autoimmune-Mediated Glomerular Diseases

Preliminary Findings From the IgA Nephropathy Cohort

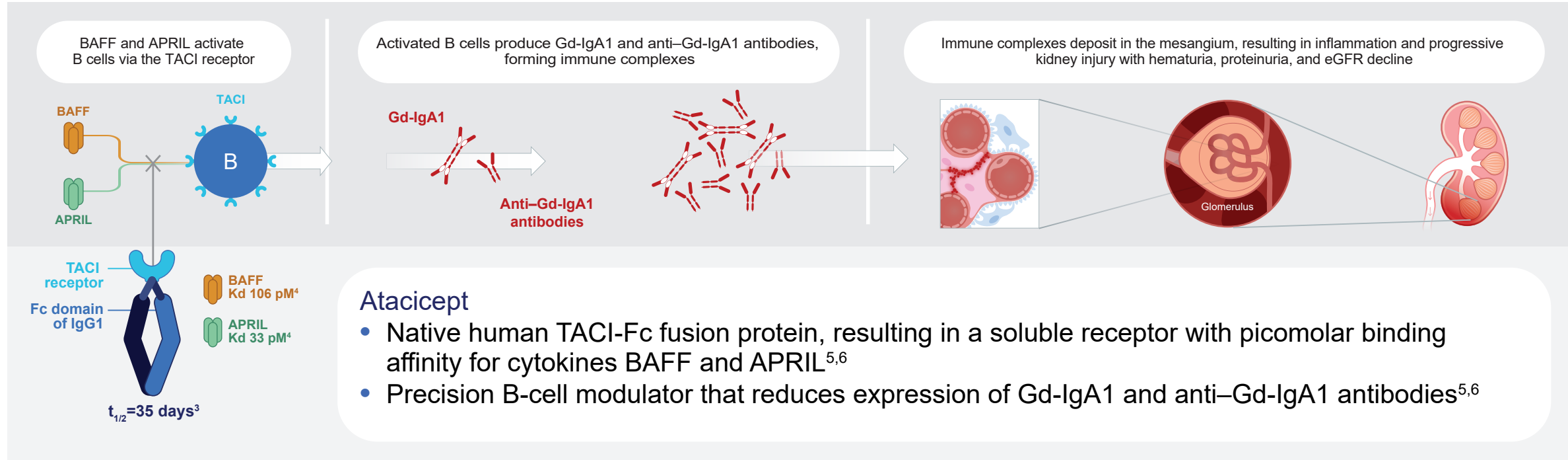
Jonathan Barratt,¹ Richard Lafayette,² Robert Brenner,³ Pamela Winterberg,³ Tao Sheng,³ James Tumlin,⁴ Glenn Chertow,⁵ Christoph Wanner⁶

¹University of Leicester, College of Medicine, Biological Sciences and Psychology, Leicester, UK; ²Glomerular Disease Center, Stanford University, Stanford, CA, USA; ³Vera Therapeutics, Inc., Brisbane, CA, USA; ⁴Department of Nephrology, Emory University School of Medicine, Atlanta, GA, USA; ⁵Departments of Medicine, Epidemiology, and Population Health, and Health Policy, Stanford University School of Medicine, Stanford, CA, USA; ⁶Department of Clinical Studies and Epidemiology, University Hospital of Würzburg, Würzburg, Germany

INTRODUCTION

Atacicept Is a Rationally Designed Fusion Protein In Late-Stage Clinical Development for the Treatment of IgAN

- IgAN is a **B-cell-mediated** immune complex glomerulonephritis associated with four disease markers^{1,2}:



In IgAN, Atacicept Has Shown Disease-Modifying Potential



In the Phase 2b trial,⁵ through 96 weeks atacicept demonstrated

- Reductions in Gd-IgA1 and proteinuria, and resolution of hematuria**
- Stabilization of eGFR** (annualized slope of -0.6 ± 0.5 mL/min/1.73 m² per year)

Safety profile was **comparable with placebo** in the double-blind period



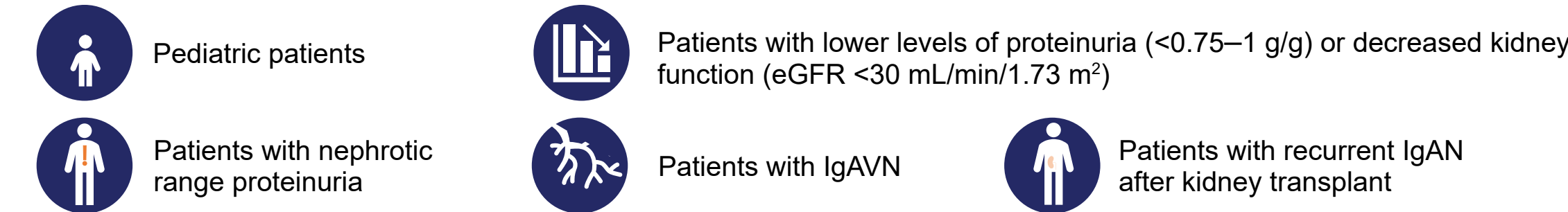
In the Phase 3 trial,⁶ atacicept at 36 weeks

- Achieved the primary endpoint** with a 46% **reduction in proteinuria**
- Reduced Gd-IgA1** by 68% and **resolved hematuria** in 81% of participants

Safety profile was **comparable with placebo** without increased risk of infection (no serious, severe, or opportunistic infections were reported)

Expanding Experience of Atacicept Across IgAN Presentation

- Clinical trials of new IgAN therapies often apply restrictive eligibility criteria, limiting translation of results to IgAN patients seen in the clinic, such as⁷:



- Importantly, even patients with low levels of proteinuria remain at risk of **progressive kidney function decline and kidney failure** over their lifetime⁸
- The **PIONEER** trial is a basket trial **evaluating atacicept across a broad range of IgAN disease presentations and stages**, as well as multiple autoimmune glomerular diseases with similar B-cell-mediated pathophysiology

Objective: to analyze preliminary efficacy data in the IgAN subpopulation of the PIONEER trial, including participants with lower proteinuria and eGFR than typical Phase 3 trials

METHODS



A global, open-label Phase 2 trial evaluating safety and efficacy of atacicept in B-cell-mediated glomerular diseases, including an expanded presentation of IgAN

Expanded IgAN cohorts

- Adults** with biopsy-proven IgAN or IgAVN
 - » Minimum eGFR 20 mL/min/1.73 m²
 - » Minimum UPCR 0.5 g/g
- Adults** with recurrent IgAN post-transplant
- Children*** (age ≥ 2 to <18 years) with biopsy-proven IgAN or IgAVN (UPCR ≥ 1 g/g)

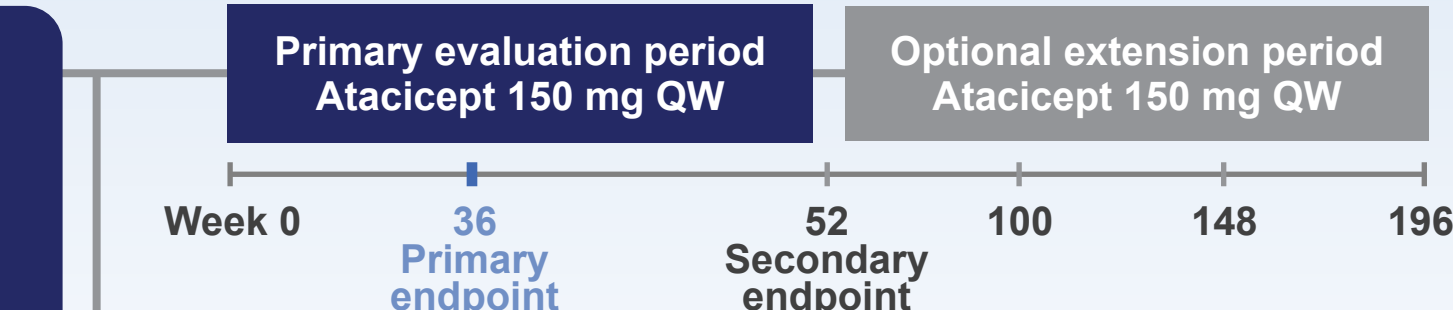
*Enrollment is being staged by age and weight pending interim analysis.

Anti-PLA2R podocytopathy (pMN)

Anti-nephrin podocytopathy (MCD/FSGS)



To learn more, contact us at clinicaltrials@veratx.com



Inclusion Criteria

- Receiving standard-of-care treatment according to local guidelines and specific requirements for each disease/cohort
- Blood pressure $\leq 160/\leq 90$ mmHg
- Weight ≥ 40 kg at screening
- Evidence of disease-specific antibodies via kidney biopsy or serological assay

Exclusion Criteria

- $\geq 50\%$ loss of eGFR within 3 months of screening
- Mixed or multiple glomerulopathies at biopsy
- Severe kidney impairment (eGFR <15 mL/min/1.73 m²), or receiving dialysis or kidney replacement therapy
- Secondary causes of glomerular disease

Primary Endpoints

- Change from baseline in UPCR at Week 36
- Safety and tolerability

Secondary Endpoints

- Change from baseline in eGFR at Weeks 36 and 52
- Change from baseline in Gd-IgA1, anti-PLA2R, or anti-nephrin antibodies

RESULTS

Baseline Demographics for Adults With IgAN*

N	81
Age, years, median (range)	42 (18, 88)
Male sex, n (%)	48 (59)
Race, n (%)	
White	57 (70)
Asian	16 (20)
Black or African American	0
Native Hawaiian/Pacific Islander	0
American Indian or Alaska Native	1 (1)
Other/not reported/unknown	7 (9)
Hispanic/Latino ethnicity, n (%)	7 (9)
eGFR, mean $\pm$ SD, mL/min/1.73 m ²	65 $\pm$ 34
UPCR by 24h urine, mean $\pm$ SE, g/g	1.0 $\pm$ 0.091

*Baseline sample includes 13 adult participants with IgAVN.

Abbreviations

APRIL=A Proliferation-Inducing Ligand; **BAFF**=B-cell Activating Factor; **CI**=confidence interval; **eGFR**=estimated glomerular filtration rate; **Fc**=fragment crystallizable; **FSGS**=focal segmental glomerulonephritis; **Gd-IgA1**=galactose-deficient immunoglobulin A1; **IgA**=immunoglobulin A; **IgAN**=IgA nephropathy; **IgAVN**=IgA vasculitis with nephritis; **IgG**=immunoglobulin G; **Kd**=dissociation constant; **MCD**=minimal change disease; **PLA2R**=phospholipase A2 receptor; **pMN**=primary membranous nephropathy; **QW**=once weekly; **SD**=standard deviation; **SE**=standard error; $t_{1/2}$ =half-life; **TACI**=transmembrane activator and calcium-modulator and cyclophilin ligand interactor; **UPCR**=urine protein-to-creatinine ratio.

KEY TAKEAWAYS



Many autoimmune glomerular diseases share a common B-cell-mediated pathophysiology



The **PIONEER** study is evaluating atacicept, a BAFF/APRIL inhibitor, across multiple autoimmune glomerular diseases including IgAN participants with lower levels of proteinuria and eGFR than typically included in clinical trials



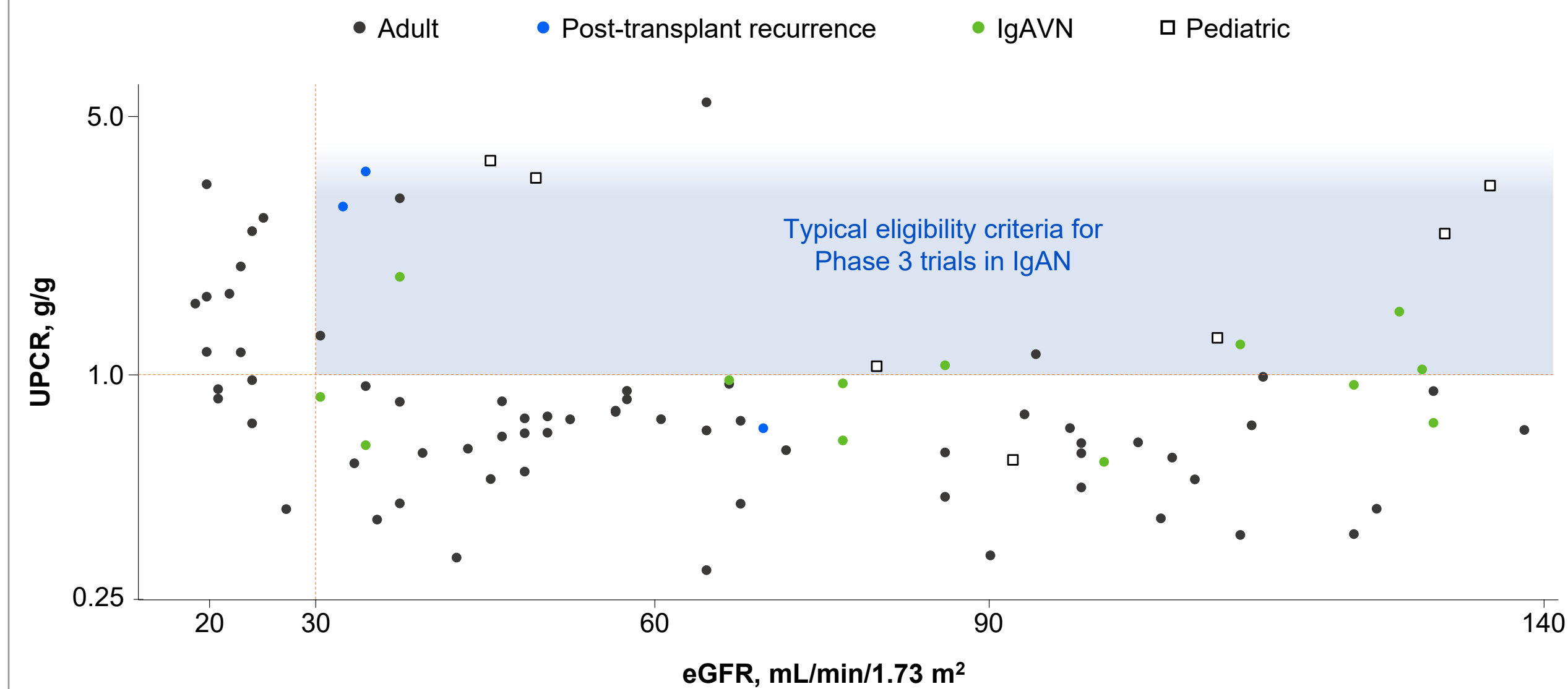
Emerging data from **PIONEER** in adults with IgAN suggest that the trend of reduction in UPCR is consistent with that observed in the atacicept arm of the **ORIGIN** clinical program

SCAN TO DOWNLOAD



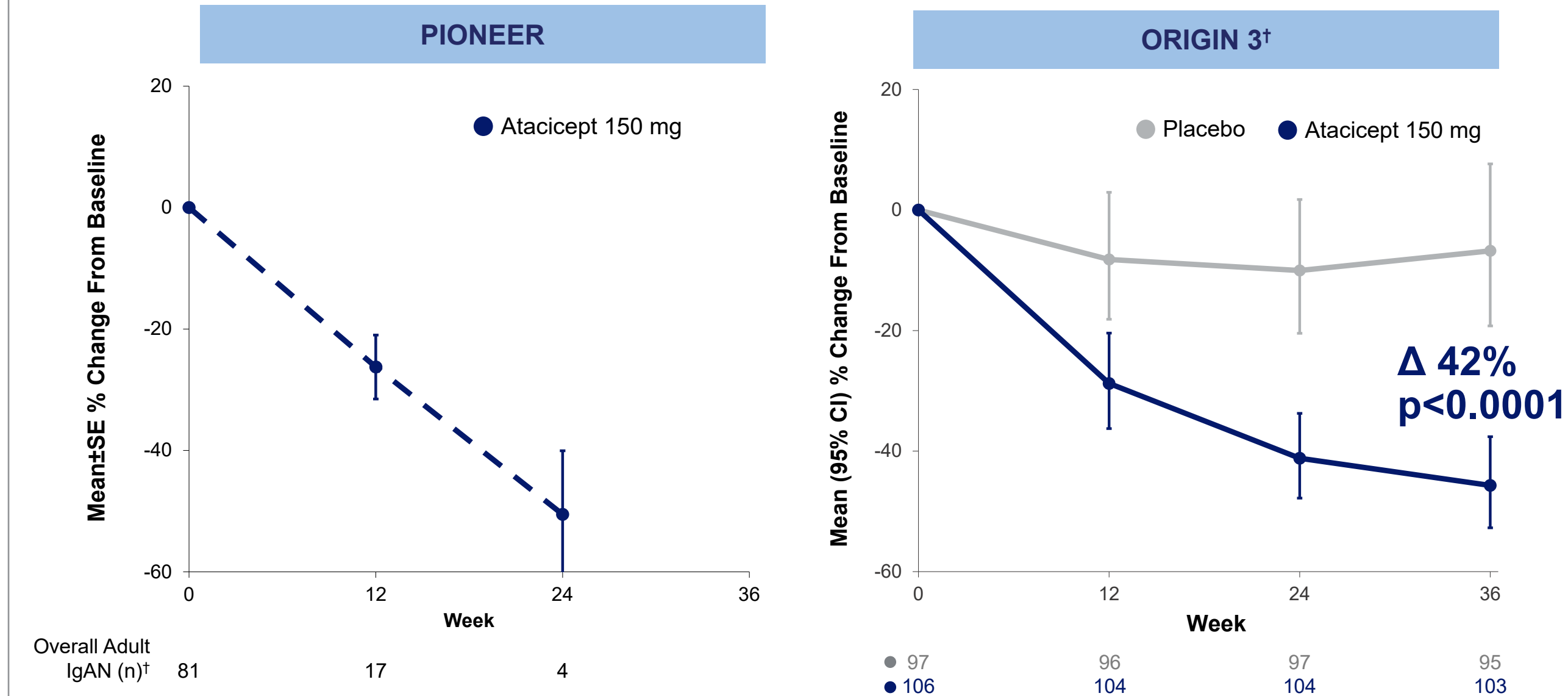
RESULTS (CONT'D)

PIONEER Has Enrolled IgAN and IgAVN Participants With Lower Proteinuria and eGFR Than Typical Phase 3 Trials



- PIONEER includes a broader range of IgAN presentations by enrolling participants with baseline eGFR and UPCR levels beyond the ranges evaluated in ORIGIN 3

UPCR Reduction in PIONEER IgAN Cohorts* and ORIGIN 3



- Emerging 24h UPCR reductions observed in adults with IgAN enrolled in PIONEER demonstrate trends comparable with those seen in ORIGIN 3

*Baseline sample includes 13 adult participants with IgAVN. *ORIGIN 3 baseline UPCR 1.7 $\pm$ 1.0.

Acknowledgments

We thank the PIONEER study volunteers and their families, and the PIONEER investigators, study staff, and collaborators. Medical writing support was sponsored by Vera Therapeutics, and provided by Mitch Lesko, PhD, of Real Chemistry.

Funding

Study was funded by Vera Therapeutics.

Contact: medinfo@veratx.com

ORIGIN EXTEND: Assessment of IgAN Disease Markers During Atacicept Off-Treatment Period

Richard Lafayette,¹ Sean Barbour,² Eric Michael,³ Kirk Campbell,⁴ Jürgen Floege,⁵ Hitoshi Suzuki,⁶ Sydney Tang,⁷ Vladimir Tesar,⁸ Hernan Trimarchi,⁹ Hong Zhang,¹⁰ Zeeshan Khawaja,³ Jonathan Barratt¹¹

¹Glomerular Disease Center, Stanford University, Stanford, CA, USA; ²The University of British Columbia, Vancouver, Canada; ³Vera Therapeutics, Inc., Brisbane, CA, USA; ⁴Icahn School of Medicine at Mount Sinai, New York, NY, USA; ⁵Rheinisch-Westfälische Technische Hochschule, Aachen University Hospital, Aachen, Germany; ⁶Juntendo University Urayasu Hospital, Chiba, Japan; ⁷Division of Nephrology, Department of Medicine, The University of Hong Kong, Hong Kong; ⁸Charles University, Prague, Czech Republic; ⁹Hospital Británico de Buenos Aires, Buenos Aires, Argentina; ¹⁰Peking University First Hospital, Beijing, P.R. China; ¹¹University of Leicester, College of Medicine Biological Sciences and Psychology, Leicester, UK

INTRODUCTION

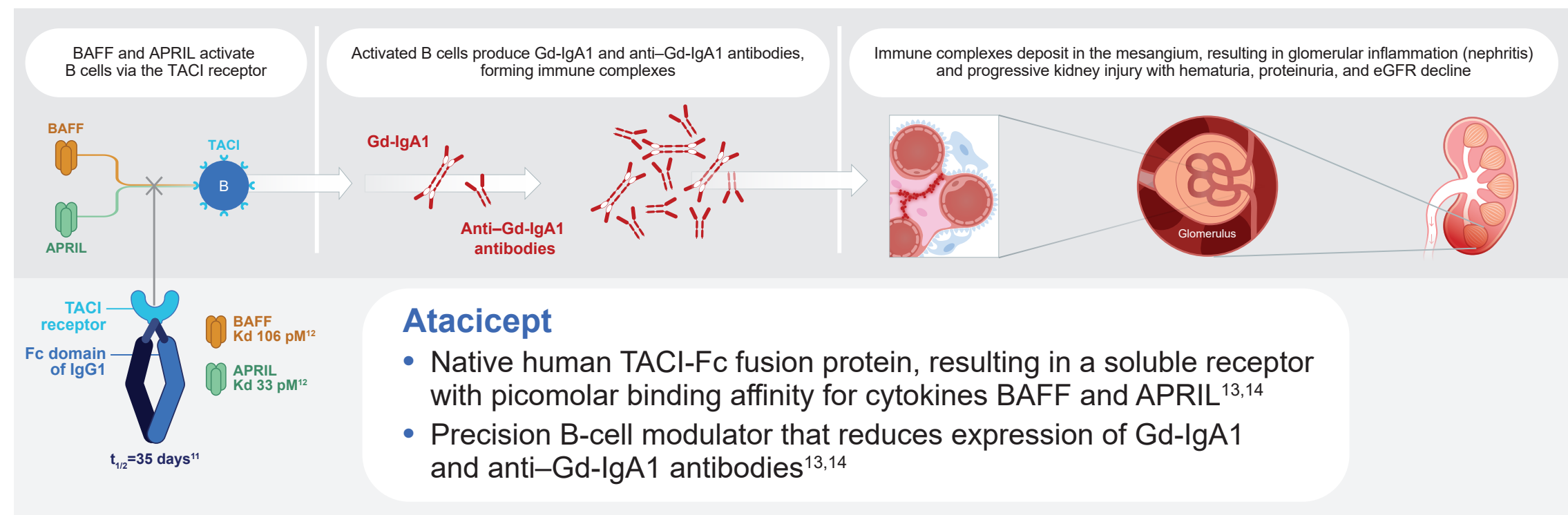
IgAN: High Unmet Need for Effective Disease-Modifying Therapies

- IgAN is a chronic, **B-cell-mediated** disease associated with a **progressive loss of kidney function**, high lifetime risk of kidney failure, and four key markers of disease¹⁻⁴



- IgAN is predominantly **diagnosed in young adults**; most patients already show signs of CKD at diagnosis, and approximately **50% require dialysis or transplant within 10–20 years of diagnosis**⁵⁻⁸
- Current treatment options have not demonstrated adequate reduction of eGFR decline to a level that minimizes the lifetime risk of kidney failure per KDIGO 2025 IgAN/IgAVN guidelines^{9,10}

Atacicept: Dual BAFF/APRIL Inhibitor



Atacicept was Assessed in IgAN in the ORIGIN trials



In the Phase 2b trial,¹³ through 96 weeks atacicept demonstrated

- Reductions in Gd-IgA1, increased resolution of hematuria, reductions in proteinuria, and stabilization of eGFR**
- Safety** profile was **comparable with placebo** in the double-blind period and remained consistent in the OLE
- No opportunistic or fatal infections occurred**, and serious infections were uncommon and resolved



Similar results¹⁴ were observed in the Phase 3 ORIGIN trial:

- Reductions in Gd-IgA1, increased resolution of hematuria, and reductions in proteinuria**, with a safety profile comparable with placebo¹⁴

This analysis presents baseline characteristics and IgAN disease markers at enrollment in ORIGIN EXTEND in participants who completed ORIGIN 2b and experienced an off-treatment interval

METHODS



ClinicalTrials.gov NCT06674577

Phase 2 OLE study in participants who complete ORIGIN 2b or ORIGIN 3

Objectives:

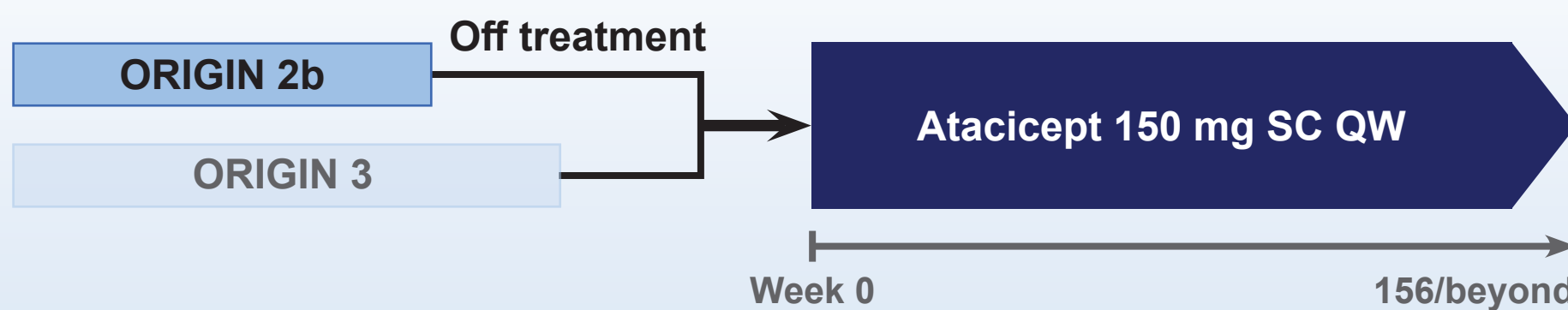
- Capture longer-term safety and efficacy data of atacicept treatment
- Generate data from reinitiation of atacicept treatment following off-treatment period

Key Inclusion Criterion

Completed the protocol-defined treatment period of a parent study of atacicept in participants with IgAN

Key Endpoints

Changes in proteinuria, hematuria, eGFR, serum Gd-IgA1 levels, and safety and adverse events



RESULTS

Baseline Characteristics

Characteristic	ORIGIN 2b Participants Enrolled in ORIGIN EXTEND (n=69)
Age, years, median (range)	42 (21, 70)
Male sex, n (%)	44 (64)
Asian race, n (%)	35 (51)
RAASI use, n (%)	60 (87)
SGLT2i use, n (%)	34 (49)
Off-treatment period, months, median (range)	16 (8, 22)

Changes in Key Disease Markers in the Atacicept Off-Treatment Period

	24-hour UPCR (g/g)			eGFR (mL/min/1.73 m ²)	
Timepoint	Value	Absolute Change	Mean % Change (SE)	Value	Mean Change (SE)
End of ORIGIN 2b treatment	0.886	+0.423	+52.6% (15.1)	58.4	-5.2 (1.7)
ORIGIN EXTEND Day 1*	1.317			53.9	

*24-hour UPCR value is from screening visit.

KEY TAKEAWAYS



IgAN is a chronic B-cell-mediated immune complex glomerulonephritis and a leading cause of kidney failure



Atacicept is a native human TACI-Fc fusion protein that inhibits BAFF and APRIL, key cytokines that drive B-cell activity central to IgAN pathophysiology



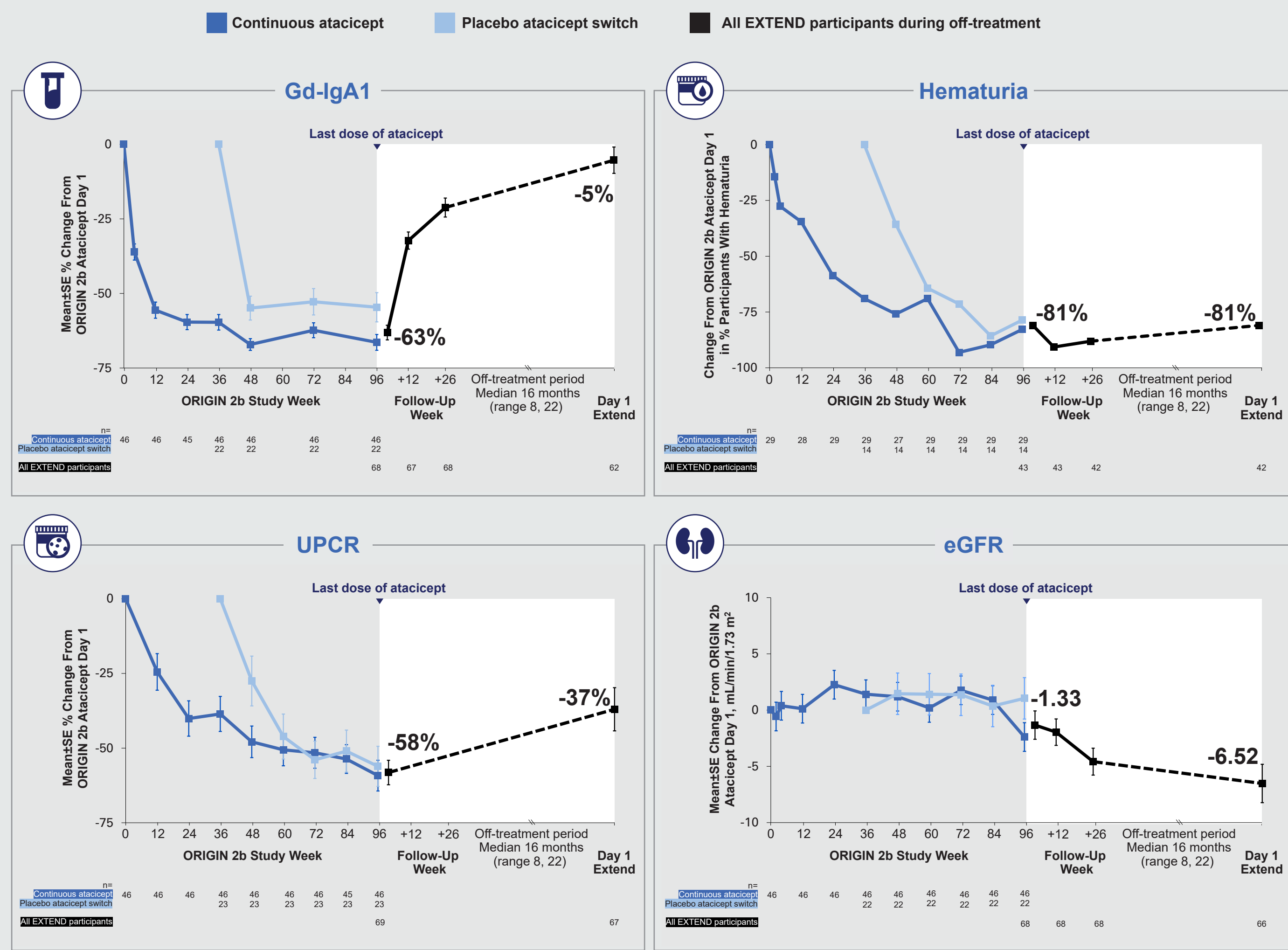
Observed worsening in markers of kidney function during the off-treatment period between ORIGIN 2b and ORIGIN EXTEND may suggest a potential benefit of chronic atacicept treatment in IgAN

SCAN TO DOWNLOAD



RESULTS (CONT'D)

Changes In Key Markers From ORIGIN 2b Day 1 to EXTEND Day 1



UPCR for continuous atacicept group is the geometric mean of all available UPCRs prior to the first dose.

Change from baseline in eGFR and percentage changes from baseline in UPCR and Gd-IgA1 were obtained from mixed-effects model for repeated measures, with natural logarithm transformation for UPCR and Gd-IgA1 values. Percentage change from baseline in patients with hematuria was obtained based on descriptive statistics.

CONCLUSIONS

Disease markers worsened across multiple IgAN parameters over a median of 16 months off therapy, despite continued standard-of-care treatment

These findings support a potential benefit of chronic atacicept treatment in IgAN

References

- Huang X, Xu G. *Front Pharmacol*. 2021;12:715253.
- Cheung CK, et al. *Front Nephrol*. 2024;3:1346769.
- Duan ZY, et al. *Biomark Res*. 2024;12:72.
- Cheung CK, et al. *Nat Rev Nephrol*. 2025;21(1):9-23.
- Kwon CS, et al. *J Health Econ Outcomes Res*. 2021;8(2):36-45.
- Pitcher D, et al. *Clin J Am Soc Nephrol*. 2023;18(6):727-738.
- Jarrick S, et al. *J Am Soc Nephrol*. 2019;30(5):866-876.
- Caster DJ, et al. *Kidney Int Rep*. 2023;8(9):1792-1800.
- KDIGO IgAN and IgAV Work Group. *Kidney Int*. 2025;108(4S):S1-S71.
- Stamellou E, et al. *Clin Kidney J*. 2025;18:sfaf324.

- Willen D, et al. *Eur J Drug Metab Pharmacokinet*. 2020;45(1):27-40.
- Data on File. Vera Therapeutics.
- Barratt J, et al. *J Am Soc Nephrol*. 2025;36(4):679-687.
- Lafayette R, et al. *N Engl J Med*. 2026;394:647-657.

Abbreviations

APRIL=A Proliferation-Inducing Ligand; **BAFF**=B-cell Activating Factor; **CKD**=chronic kidney disease; **eGFR**=estimated glomerular filtration rate; **Fc**=fragment crystallizable; **Gd-IgA1**=galactose-deficient IgA1; **IgA**=immunoglobulin A; **IgAN**=IgA nephropathy; **IgAVN**=IgA vasculitis with nephritis; **IgG**=immunoglobulin G; **Kd**=dissociation constant; **KDIGO**, Kidney Disease: Improving Global Outcomes; **OLE**=open-label extension; **QW**=once weekly; **RAASI**=renin-angiotensin-aldosterone system inhibitor; **SC**=subcutaneous; **SE**=standard error; **SGLT2i**=sodium-glucose cotransporter-2 inhibitor; **t_{1/2}**=half-life; **TACI**=transmembrane activator and calcium-modulator and cyclophilin ligand interactor; **UPCR**=urine protein-to-creatinine ratio.

Acknowledgments

We thank the ORIGIN Phase 2b study volunteers and their families, and the ORIGIN investigators, study staff, and collaborators. Medical writing support was sponsored by Vera Therapeutics, and provided by Ricardo Estupinan, PhD, of Real Chemistry.

Funding

Study was funded by Vera Therapeutics.

Contact: medinfo@veratx.com