vera therapeutics

R&D Day

January 25, 2024

Forward-Looking Statements

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Certain data in this presentation are based on cross-study comparisons and are not based on any head-to-head clinical trials. Cross-study comparisons are inherently limited and may suggest misleading similarities or differences.

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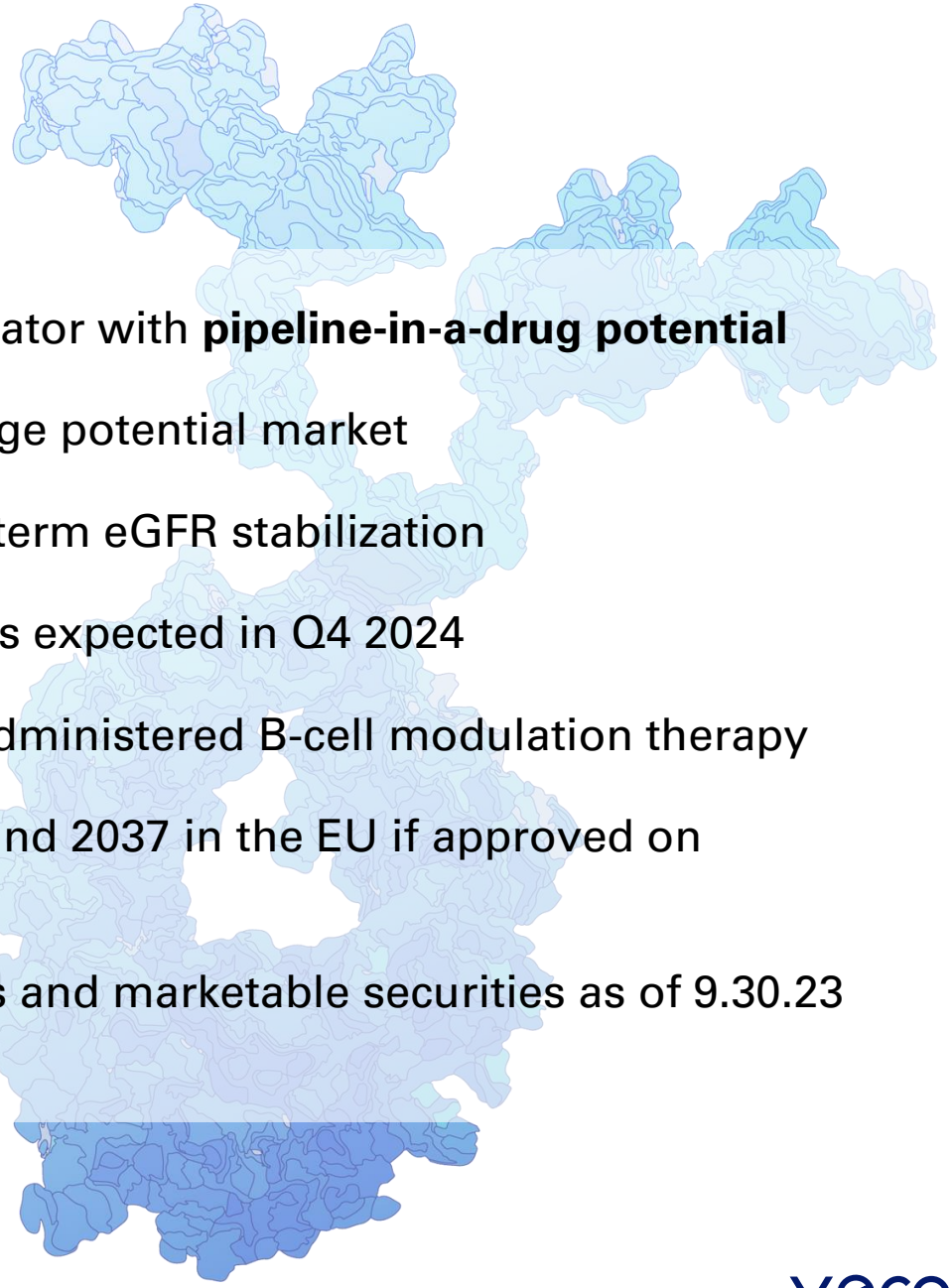
Agenda

Opening Remarks	**Marshall Fordyce, MD** Founder and CEO, Vera Therapeutics
IgAN Disease State	**Jonathan Barratt, PhD, FRCP** Professor, University of Leicester
Atacicept ORIGIN Phase 2b 72 Week Results	**Richard Lafayette, MD, FACP** Professor, Stanford University
Closing Remarks	**Robert Brenner, MD** Chief Medical Officer, Vera Therapeutics
Q&A	

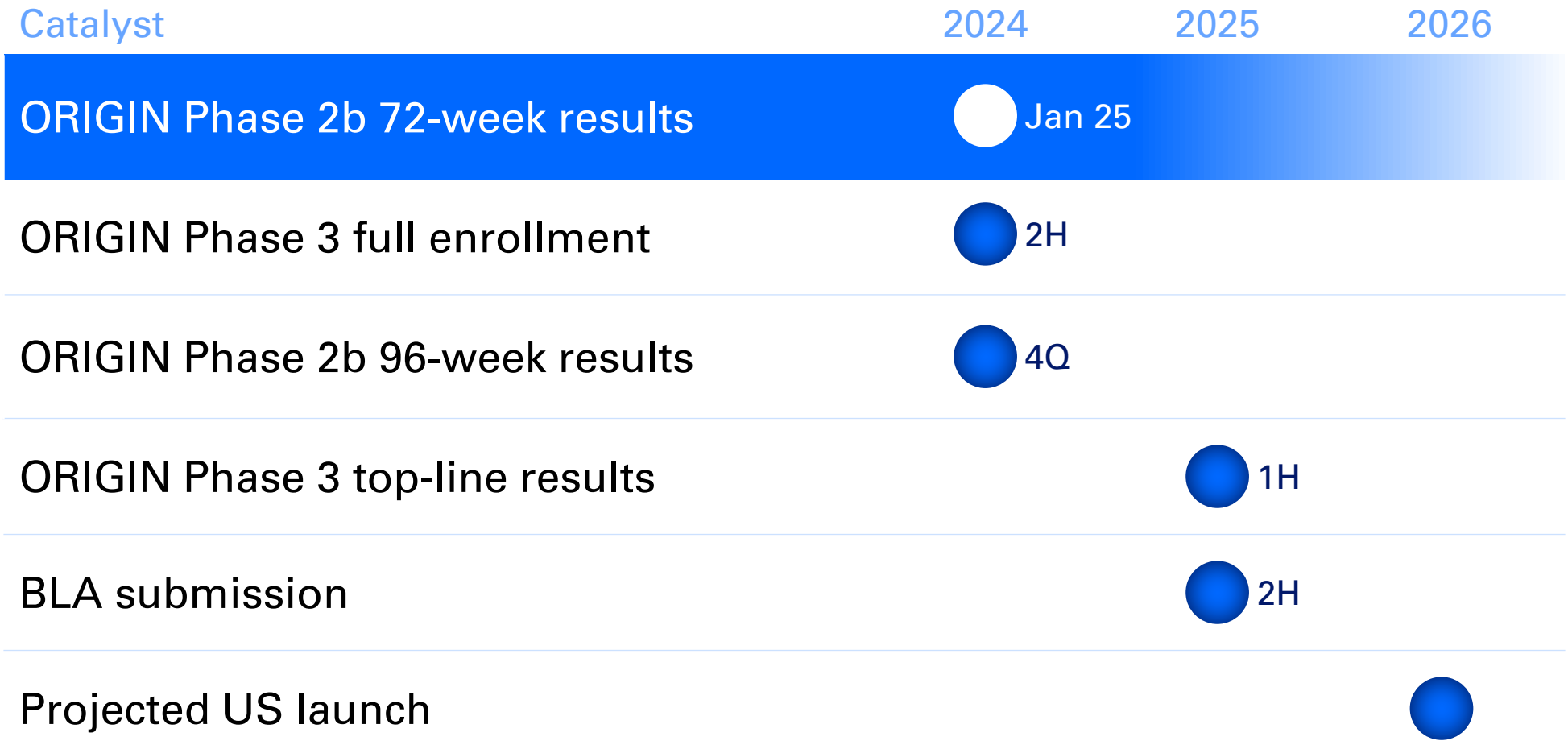
Corporate Highlights



- **Atacicept** is a potential first-in-class dual BAFF/APRIL B cell modulator with **pipeline-in-a-drug potential**
- Currently in Phase 3 pivotal trial for **IgA Nephropathy (IgAN)**, a large potential market
- Differentiation based on **disease-modifying MOA**, evident in long-term eGFR stabilization
- ORIGIN Phase 2b 72-week results **presented today;** 96-week results expected in Q4 2024
- Phase 3 readout expected 1H 2025, potential **first-to-market** self-administered B-cell modulation therapy
- Regulatory data exclusivity expected to extend to 2038 in the US and 2037 in the EU if approved on anticipated timeline
- Strong financial profile, ~$185M[1] pro forma cash, cash equivalents and marketable securities as of 9.30.23 sufficient to **fund IgAN-focused operations to 2026**

1. Unaudited; *pro forma* cash includes ~$160M of cash, cash equivalents and marketable securities as of September 30, 2023 in addition to the $25M drawdown of credit facility in December 2023.
APRIL = A proliferation-inducing ligand; BAFF = B-cell activating factor; eGFR = estimated glomerular filtration rate; MOA = mechanism of action.

Atacicept: Expected Value Creation Catalysts Over Next 18 Months



Vera holds worldwide, exclusive rights to develop and commercialize atacicept

Based on management's current assumptions.

Management Team: Successful Clinical and Commercial Track Record

Marshall Fordyce, MD
President and CEO

- >15 years drug dev leadership
- 7 new drug approvals, Project Lead for tenofovir alafenamide program

GILEAD

Sean Grant, MBA
Chief Financial Officer

- >15 years in corporate strategy, finance, and capital raising
- Former healthcare banker with capital raising and M&A experience

CareDx® Your Partner in Transplant Care™ citi

Robert Brenner, MD
Chief Medical Officer

- Nephrologist with >25 years biotech leadership supporting multiple drug approvals

AMGEN amag PHARMACEUTICALS

William Turner
Chief Development Officer

- ~30 years drug dev and commercialization leadership in multiple therapeutic areas

SIERRA ONCOLOGY DYNAVAX aimmune THERAPEUTICS

Lauren Frenz, MBA
Chief Business Officer

- >15 years industry experience, including global commercial planning and multiple blockbuster launches at Gilead
- Strategic advisory at Leerink

GILEAD LEERINK PARTNERS

Kelly Rauber
VP, Head of HR

- >18 years in-depth HR experience from multiple industries

CYTOMX ORIC

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Strong Financial Position

~$185M

Pro forma cash, cash equivalents, and marketable securities including $25M drawdown of credit facility[1]

Current capital position sufficient to fund IgAN-focused operations to

2026

~44.4M

Shares outstanding
(as of 9.30.23)

1. Unaudited; *pro forma* cash includes ~$160M of cash, cash equivalents and marketable securities as of September 30, 2023 in addition to the $25M drawdown of credit facility in December 2023.

Vera Pipeline: Compelling Late-Stage Opportunities For Patient Benefit

Atacicept

Lead Indication: **IgAN**	Phase 3 Ongoing
IgAN extended dosing	Phase 2/3 potential
LN	Phase 3 ready
SLE	Phase 3 ready
Sjogren's syndrome	Phase 3 potential
Myasthenia gravis	Phase 3 potential
Membranous nephropathy	Phase 3 potential

MAU868

BK virus in transplantation	Phase 2/3 potential

LN = lupus nephritis; SLE = Systemic lupus erythematosus.

MAU868: Novel Investigational Neutralizing Antibody Targeting BK Virus

Phase 2 Trial in Kidney Transplantation: Markedly decreased BK viral load and stable eGFR

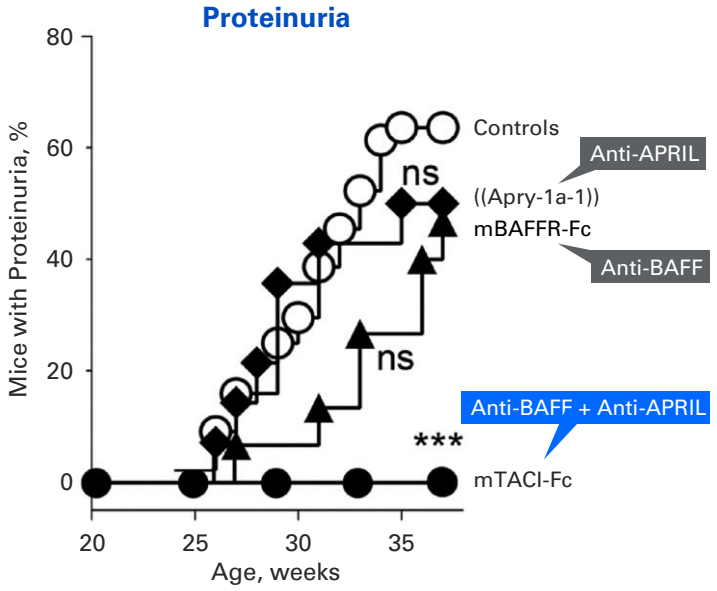
	MAU868 n=20	Placebo n=8	P-value
Log reduction in BK viremia, median (IQR) DNA copies/mL	-1.14 (-1.88, -0.50)	0.37 (-0.72, 0.04)	0.051
Patients with reduction in BK plasma viral load, n (%)			
by ≥1 log	11 (55)	1 (13)	0.040
to <lower limit of quantification	4 (20)	0	0.172
to $<10^4$ DNA copies/mL	15 (75)	3 (38)	0.061
Change in eGFR, median (IQR) mL/min/1.73m^2	2.0 (-5.0, 4.0)	-6.0 (-8.5, -0.5)	0.217

Jordan S, et al. Am J Transplant 2022.

Atacicept Dual Cytokine Inhibition of BAFF and APRIL:

Superior Potential B cell Modulation vs Single Pathway Intervention

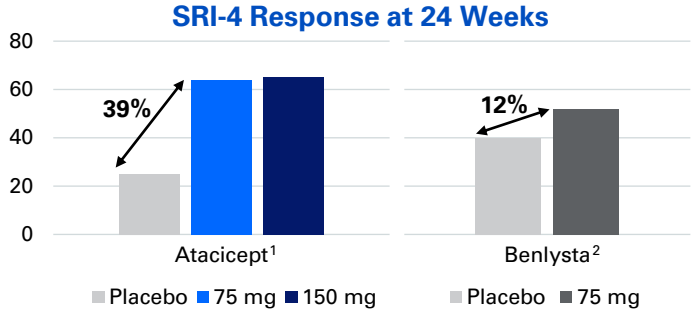
Pre-Clinical Evidence:
BAFF-APRIL >> BAFF or APRIL alone



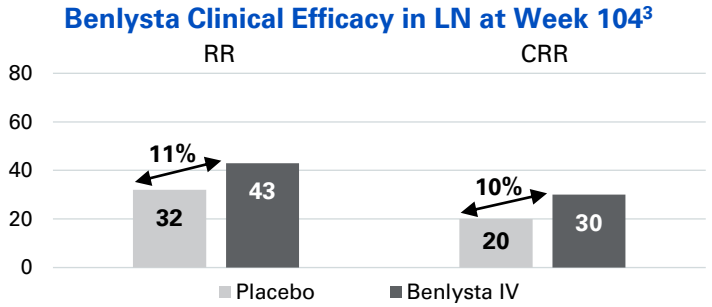
In mouse model of LN, atacicept prevented proteinuria compared to BAFF or APRIL alone

***p<0.001. Haselmayer P, et al. Eur J Immunol 2017.

Clinical Evidence:
BAFF-APRIL >> BAFF or APRIL alone



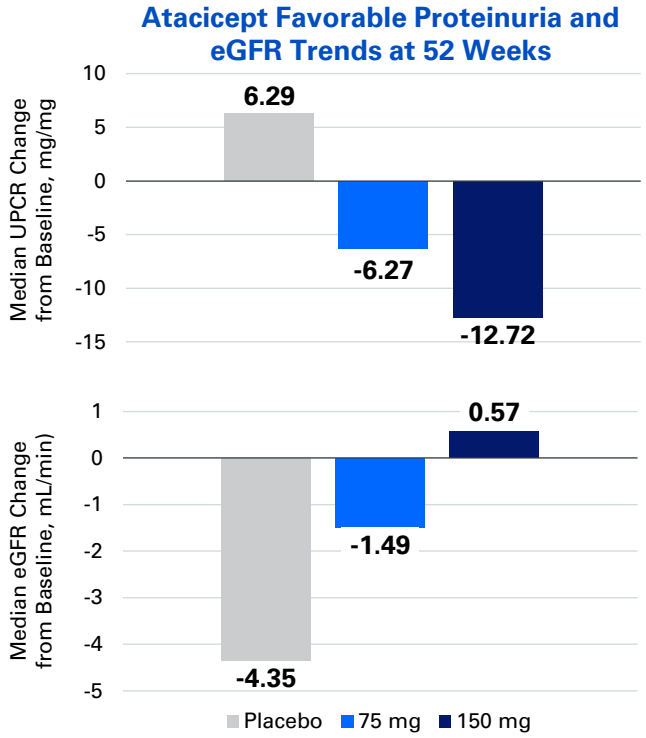
In similar serologically active SLE patients, BAFF/APRIL inhibition may provide better efficacy vs BAFF alone*



BENLYSTA approved in LN, but RR still <50%; we believe there is room for improvement with dual blockade[3]

1. Merrill JT, et al. Arthritis Rheumatol 2018; 2. van Vollenhoven RF, et al. Ann Rheum Dis 2012; 3. Furie R, et al. N Engl J Med 2020.

Clinical Evidence:
Improved kidney function in SLE



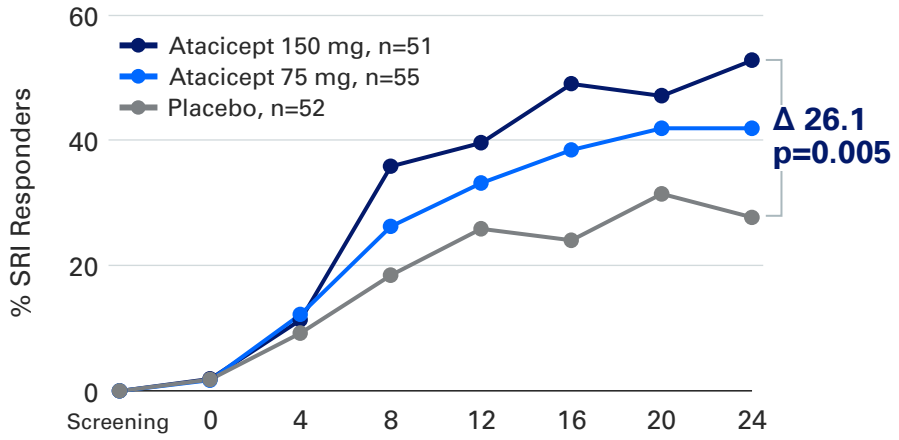
Phase 2 atacicept APRIL-SLE trial showed improved eGFR and proteinuria trends at 1 year in moderate–severe SLE

Isenberg D, et al. ERA-EDTA 2022 oral.

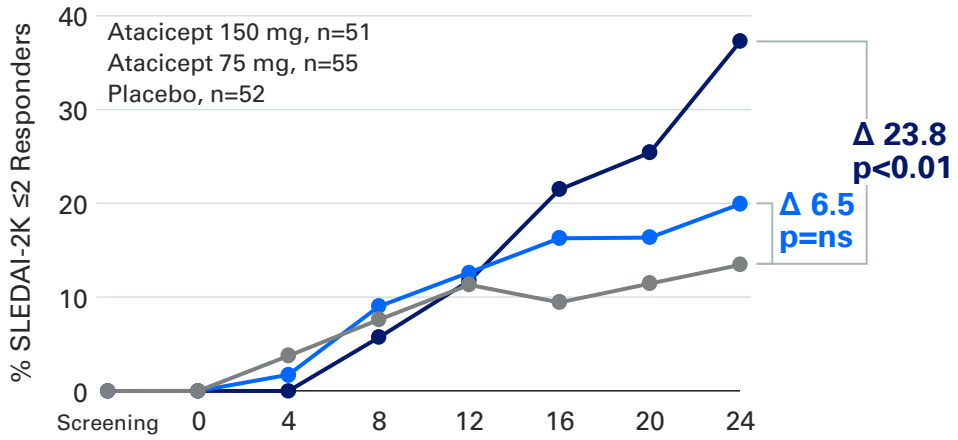
***Based on a cross-trial comparison and not a head-to-head clinical trial, such data may not be directly comparable due to differences in study protocols, conditions and patient populations.**
CRR = complete renal response; RR = renal response; UPCR = urine protein:creatinine ratio.

Atacicept Phase 2 Results in SLE Potentially Best-In-Class Clinical Activity

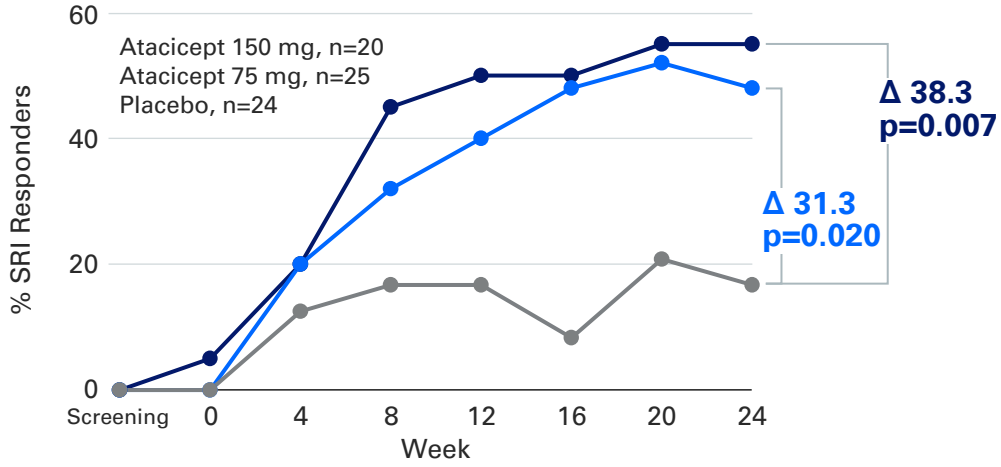
SRI-6 Response in HDA Patients (n=158)[1,2]



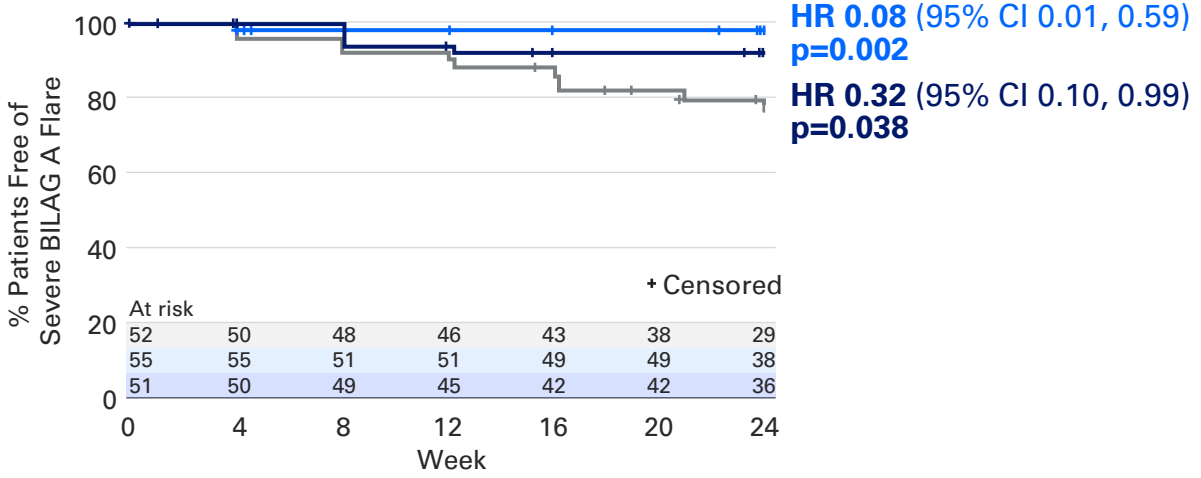
HDA Patients Reaching LDA (n=158)[3]



SRI-6 Response in HDA, Serologically Active Patients (n=69)[1,2]



Severe BILAG A Flare in HDA Patients (n=158)[2]



HDA = High Disease Activity (SLE Disease Activity Index 2000 [SLEDAI-2K] ≥10); LDA = Low Disease Activity (SLEDAI-2K ≤2). 1. SLE responder index 6 (SRI-6) response defined as ≥6-point reduction in Safety of Estrogens in Lupus Erythematosus National Assessment version of SLEDAI score, no new British Isles Lupus Assessment Group (BILAG) A organ domain score or 2 new BILAG B organ domain scores, and no worsening (<0.30-point increase) in Physician's Global Assessment (PGA) score; 2. Merrill JT, et al. Arthritis Rheumatol 2018; 3. Morand EF, et al. Rheumatology 2020.

Attractive Target Commercial Atacicept Product Profile

- Self-administration (subcutaneous) of small volume (1 mL) once weekly via autoinjector at commercial launch
- Smallest volume among B-cell modifying drugs in Phase 3 development (2–4 mL with APRIL-only)
- Large subcutaneous injection volumes are associated with pain and may affect tolerability and adherence[1]

1. Usach I, et al. Adv Ther 2019;36:2986-96. Atacicept is investigational and has not been approved by any regulatory authorities for any use.

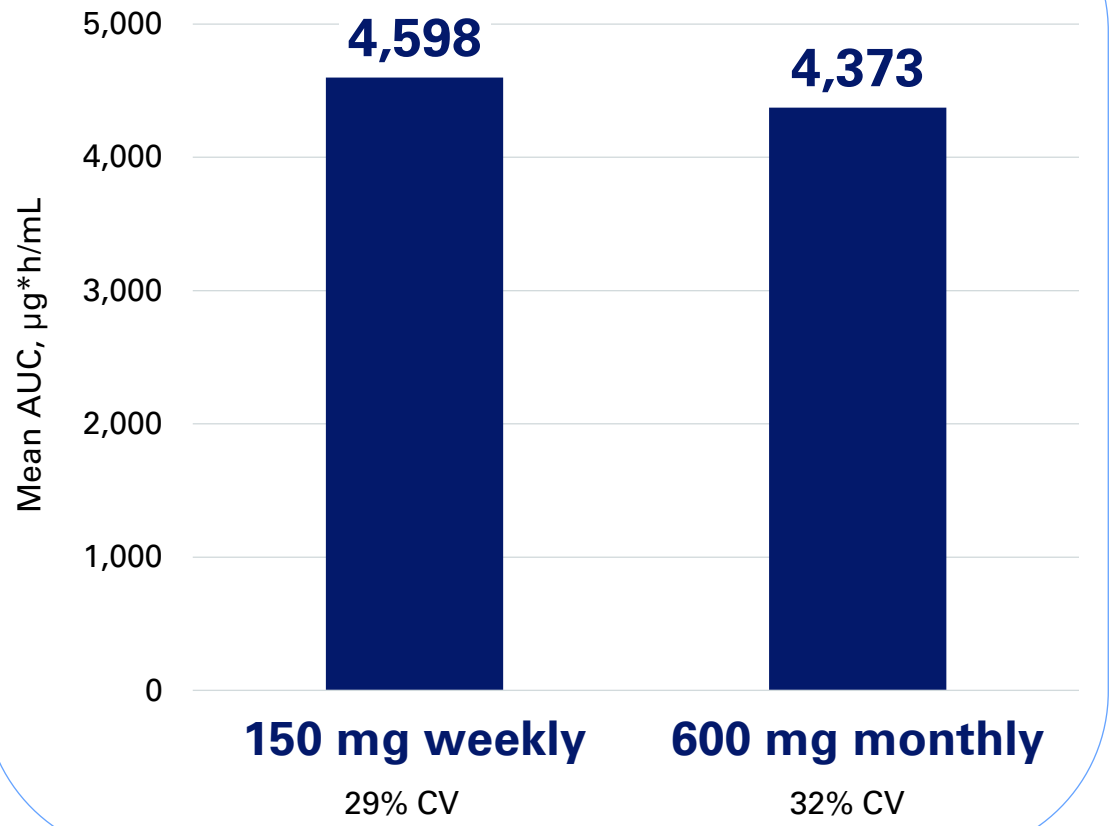
Atacicept PK/PD Supports Once-Monthly Dosing

Plan to Evaluate as Part of Life Cycle Management

Atacicept 150 mg weekly (Phase 2/3 dosing)

52 Week Simulation

Atacicept 600 mg monthly



Simulation of N=500 for each dosing scenario. AUC = area under curve; CV = coefficient of variation; PK/PD = pharmacokinetics/pharmacodynamics.

IgAN: High Unmet Need and Significant Commercial Opportunity

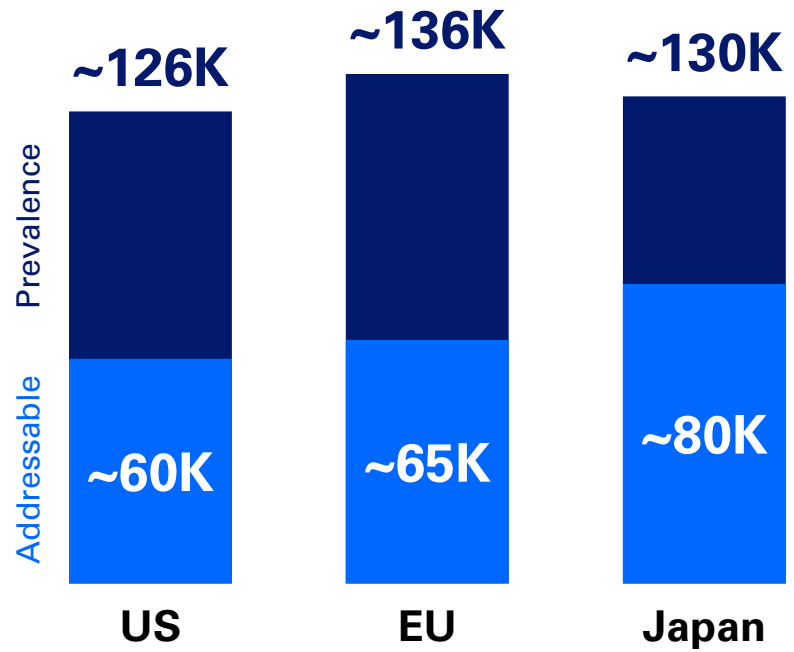
Serious and progressive autoimmune disease of the kidney; average age of diagnosis ~35 years old, severely impacting quality of life[1]

Orphan disease indication in the US and EU[2]

Up to 50% of IgAN patients progress to **ESKD**, resulting in need for **dialysis or transplant**[3,4]

Current SOC includes RASi and supportive care[5]; high unmet need for **disease-modifying therapy that targets the source**[5,6]

~$6–10B Annual Market Opportunity in US, EU, and Japan for Novel IgAN Therapeutics[7]

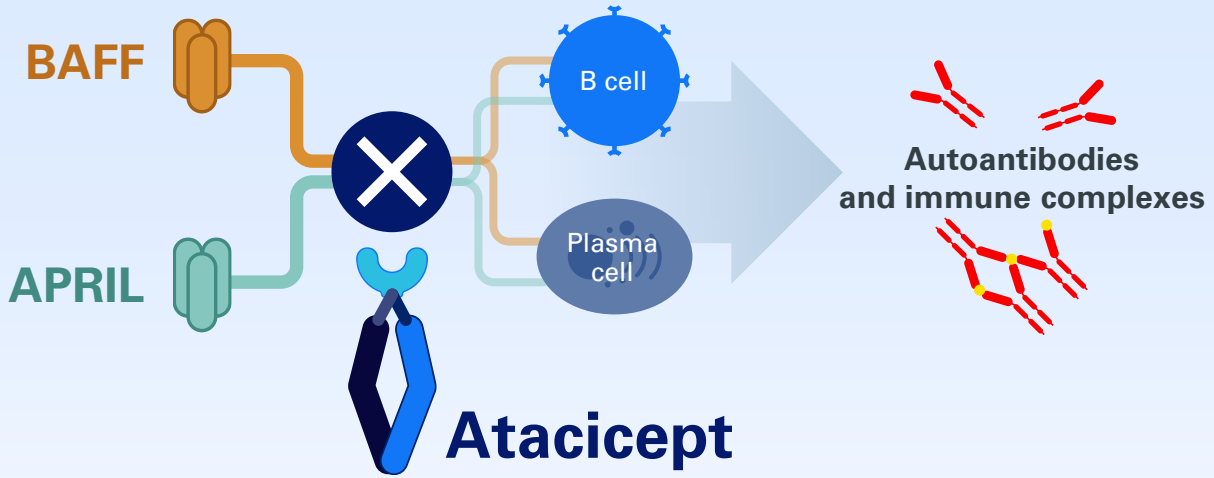


ESKD = end-stage kidney disease; RASi = renin-angiotensin system inhibitor; SOC = standard of care.

1. Jarrick S, et al. J Am Soc Nephrol 2019; 2. Orphan Disease Designation not yet obtained for atacicept in IgAN; 3. Kwon CS, et al. J Health Econ Outcomes Res 2021; 4. Pitcher D, et al. Clin J Am Soc Nephrol 2023; 5. Maixnerova D, et al. J Clin Med 2022;11:2810; 6. Huang X, Xu G. Front Pharmacol 2021;12:715253; 7. ClearView Healthcare Partners Analysis. Prevalence and addressable population estimates based on peak year forecast.

Thesis That Drove Vera Acquisition of Atacicept in 2020…

Rationale for Dual Inhibition of BAFF + APRIL with Atacicept

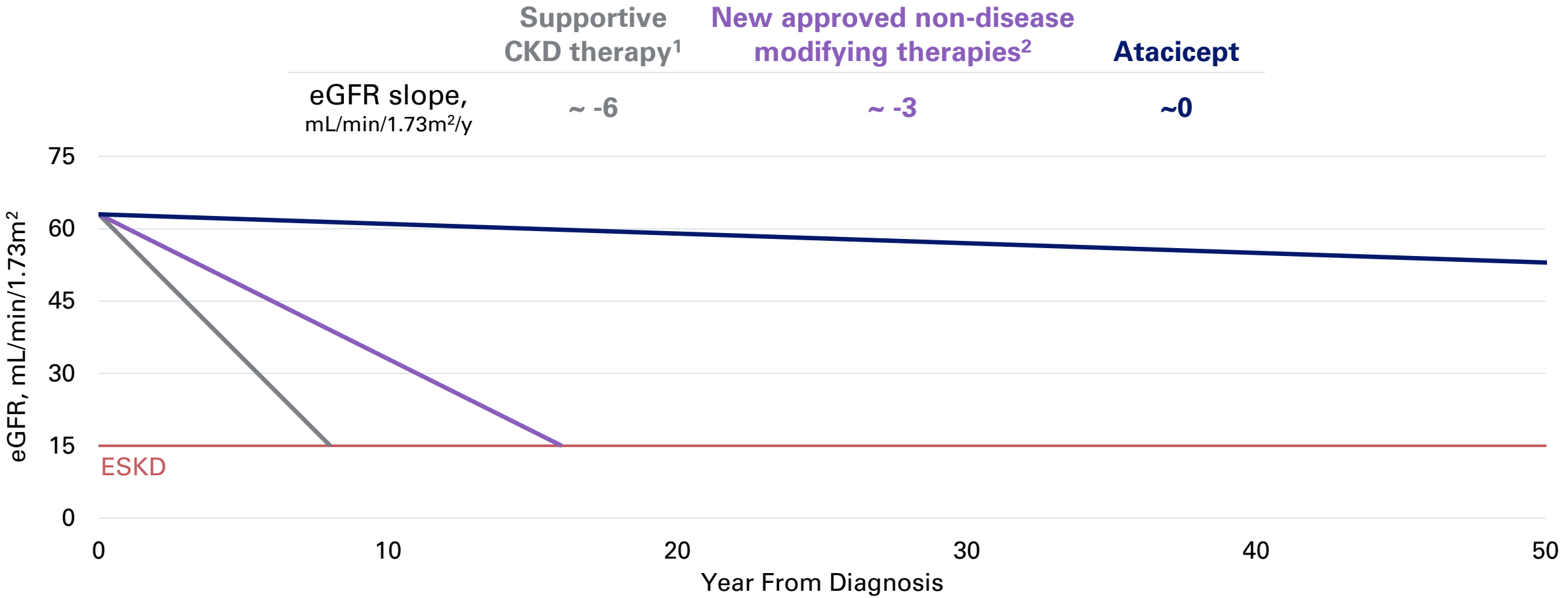


- Elevated BAFF plays **key role in IgAN pathogenesis**
  - BAFF and APRIL levels are both elevated in patients with IgAN and are each associated with clinical severity[1-3]
  - In preclinical models, overexpression of BAFF alone can lead to the development of kidney IgA deposits and IgA-like nephritis[4]
  - BAFF can directly increase the expression of factors associated with fibrosis and inflammation in mesangial cells[2]
  - Dual blockade of BAFF and APRIL decreased renal damage in an immunologic animal model more than individual blockade of either pathway alone[5]
- Dual inhibition offers the potential for **sustained clinical efficacy**
  - BAFF or APRIL alone are each capable of independently supporting plasma cell survival[5,6]
  - Blocking both biologic targets may avoid compensatory increase in parallel signal[7,8]
  - Blocking APRIL alone may lead to upregulation of BAFF signaling with potential consequences on efficacy[9]

1. Xin G, et al. J Nephrol 2013; 2. Cao Y, et al. Mol Med Rep 2020; 3. Zhai Y, et al. Medicine (Baltimore) 2016; 4. McCarthy D, et al. J Clin Invest 2011; 5. Haselmayer P, et al. Eur J Immunol 2017; 6. Benson M, et al. J Immunol 2008; 7. Yeh T, et al. J Allergy Clin Immunol 2020; 8. Vallerskog T, et al. Arthritis Res Ther 2006.

… Included Bold Projections for IgAN Disease Modification

Atacicept Potential to Convert eGFR Rate of Decline to That of the General Population



Projected eGFR trajectories do not represent clinical data and assume a constant eGFR slope over time.
Average slope estimates were applied to mean baseline eGFR of 63 mL/min/1.73m² in the ORIGIN Phase 2b study population and projected to ESKD (eGFR 15 mL/min/1.73m²).
1. Average historical placebo (including standard of care) data from 7 clinical trials[3-11]; 2. Average data from clinical trials of two therapies[3,4,10]; 3. Lafayette R, et al. Lancet 2023; 4. Travere Corporate Overview January 2024; 5. Li PK-T, et al. Am J Kidney Dis 2006; 6. Manno C, et al. Nephrol Dial Transplant 2009; 7. Lv J, et al. JAMA 2017; 8. Wheeler DC, et al. Kidney Int 2021; 9. Lv J, et al. JAMA 2022; 10. Zhang H, et al. ASN Kidney Week 2023, poster TH-PO1123; 11. Mathur M, et al. N Engl J Med 2023.

Agenda

Opening Remarks	**Marshall Fordyce, MD** Founder and CEO, Vera Therapeutics
IgAN Disease State	**Jonathan Barratt, PhD, FRCP** Professor, University of Leicester
Atacicept ORIGIN Phase 2b 72-week Results	**Richard Lafayette, MD, FACP** Professor, Stanford University
Closing Remarks	**Robert Brenner, MD** Chief Medical Officer, Vera Therapeutics
Q&A	

Jonathan Barratt, PhD, FACP

UNIVERSITY OF LEICESTER

Dr. Barratt leads the Renal Research Group within the College of Life Sciences, University of Leicester. His research is focused on a bench-to-bedside approach to improving our understanding of the pathogenesis of IgAN, a common global cause of kidney failure. Dr. Barratt is the IgAN Rare Disease Group lead for the UK National Registry of Rare Kidney Diseases (RaDaR), and a member of the steering committee for the International IgAN Network. He works closely with pharmaceutical companies interested in new treatments for IgAN, is Chief Investigator for a number of international randomized controlled Phase 2 and 3 clinical trials in IgAN, and was a member of the U.S. Food and Drug Administration and American Society of Nephrology Kidney Health Initiative: Identifying Surrogate Endpoints for Clinical Trials in IgAN Workgroup.

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Leicester IgA Nephropathy Research Group

IgA Nephropathy

Current Challenges and Unmet Needs

Professor Jonathan Barratt
University of Leicester
&
John Walls Renal Unit, Leicester

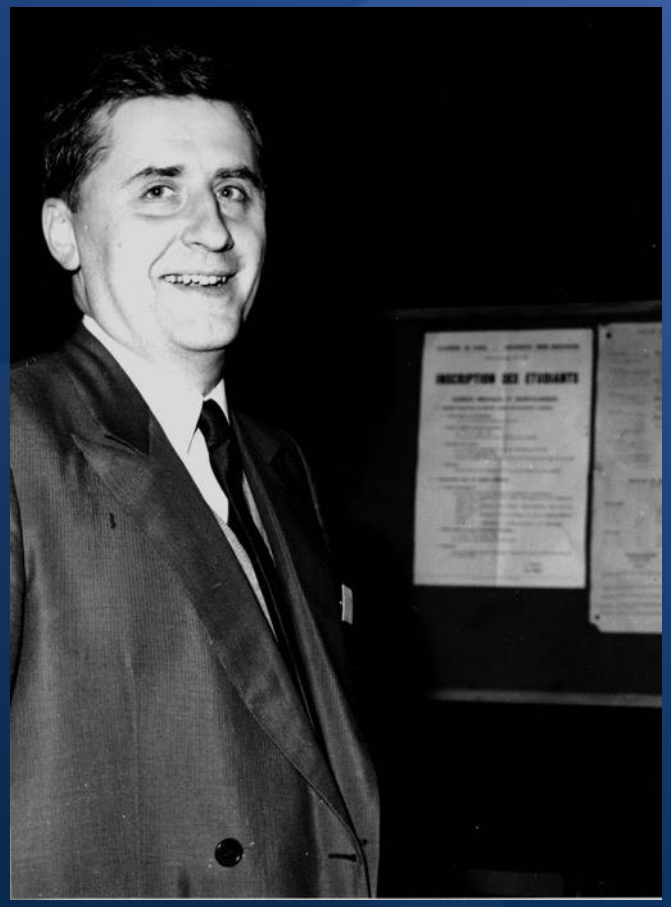
UNIVERSITY OF LEICESTER

Leicester IgA Nephropathy Research Group

Speaker Declarations

Jonathan Barratt	
Consulting and Speaker Fees	Alnylam, Argenx, Astellas, BioCryst, Calliditas, Chinook, Dimerix, Galapagos, Novartis, Omeros, Travere Therapeutics, Vera Therapeutics, Visterra
Grant Support	Argenx, Calliditas, Chinook, Galapagos, GlaxoSmithKline, Novartis, Omeros, Travere Therapeutics, Visterra
Clinical trials	ADU-CL-19 & ALIGN (Chinook), APPLAUSE (Novartis), ARTEMIS-IGAN (Omeros), ENVISION (Visterra), NefIgARD (Calliditas), ORIGIN (Vera Therapeutics)
Research projects	Argenx, Calliditas, Chinook, Galapagos, GlaxoSmithKline, Novartis, Omeros, Travere Therapeutics, Visterra

JEAN BERGER (1930-2011)



Renal Fellow Network

The French pathologist who first recognised IgA nephropathy

IgA nephropathy

used to be called

‘Berger’s disease’

Weir MR, et al. Am J Nephrol 2010

John Paul Jones (1747–1792)

J.o.P. **17** (3) 2005: 145-152

THE ILLNESSES OF PRINCE JOSEPH HABSBURG (1776-1847) AND HIS FIRST WIFE, PRINCESS ALEXANDRA PAVLOVNA ROMANOVA (1783-1801)

L. G. Józsa *

Abstract.

This study describes histological alterations in the bodies of Prince Joseph Habsburg (1776-1847) and his first wife Alexandra Pavlovna Romanova (1783-1801). Both corpses were mummified, while the internal organs were stored separately in rosemary oil in metal vessels. Royal Prince Joseph Habsburg died on 13 January 1847. The microscopic study confirms focal subacute glomerulonephritis (type Berg) with Ig A precipitate on the glomerular mesangium and Bowmann's capsule. To the author's best knowledge, this is the first case in the paleopathological literature in which the subacute Ig A glomerulonephritis could confirmed immunohistochemically. Gout (urate nephropathy), severe arteriosclerosis, prostate adenoma, and purulent prostatitis were also diagnosed. The Prince's first wife (Alexandra Pavlovna Romanova) died after childbirth at age 18, along with her newborn daughter. Histological examination of Alexandra's organs revealed severe fibrocaseous and miliary tuberculosis with dissemination to the kidneys and liver.

Long-Term Outcomes in IgA Nephropathy

David Pitcher[1,2] *Fiona Braddon*[1] *Bruce Hendry*[3] *Alex Mercer*[4] *Kate Osmaston*[1] *Moin A. Saleem*[5] *Retha Steenkamp*[1] *Katie Wong*[1,2] *A. Neil Turner*[6] *Kaijun Wang*[3] *Daniel P. Gale*[2] *and Jonathan Barratt*[7]

Abstract

Background IgA nephropathy can progress to kidney failure, and risk assessment soon after diagnosis has advantages both for clinical management and the development of new therapeutics. We present relationships among proteinuria, eGFR slope, and lifetime risks for kidney failure.

Methods The IgA nephropathy cohort (2299 adults and 140 children) of the UK National Registry of Rare Kidney Diseases (RaDaR) was analyzed. Patients enrolled had a biopsy-proven diagnosis of IgA nephropathy plus proteinuria >0.5 g/d or eGFR <60 ml/min per 1.73 m^2. Incident and prevalent populations and a population representative of a typical phase 3 clinical trial cohort were studied. Analyses of kidney survival were conducted using Kaplan–Meier and Cox regression. eGFR slope was estimated using linear mixed models with random intercept and slope.

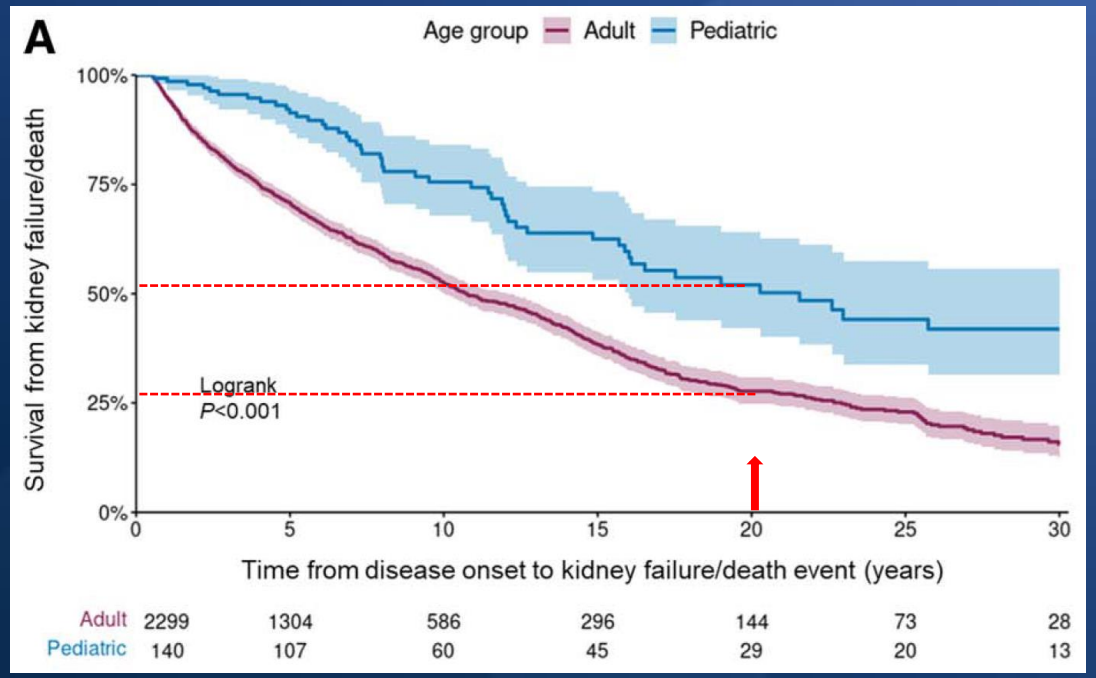
Results The median (Q1, Q3) follow-up was 5.9 (3.0, 10.5) years; 50% of patients reached kidney failure or died in the study period. The median (95% confidence interval [CI]) kidney survival was 11.4 (10.5 to 12.5) years; the mean age at kidney failure/death was 48 years, and most patients progressed to kidney failure within 10–15 years. On the basis of eGFR and age at diagnosis, almost all patients were at risk of progression to kidney failure within their expected lifetime unless a rate of eGFR loss ≤1 ml/min per 1.73 m^2 per year was maintained. Time-averaged proteinuria was significantly associated with worse kidney survival and more rapid eGFR loss in incident, prevalent, and clinical trial populations. Thirty percent of patients with time-averaged proteinuria of 0.44 to <0.88 g/g and approximately 20% of patients with time-averaged proteinuria <0.44 g/g developed kidney failure within 10 years. In the clinical trial population, each 10% decrease in time-averaged proteinuria from baseline was associated with a hazard ratio (95% CI) for kidney failure/death of 0.89 (0.87 to 0.92).

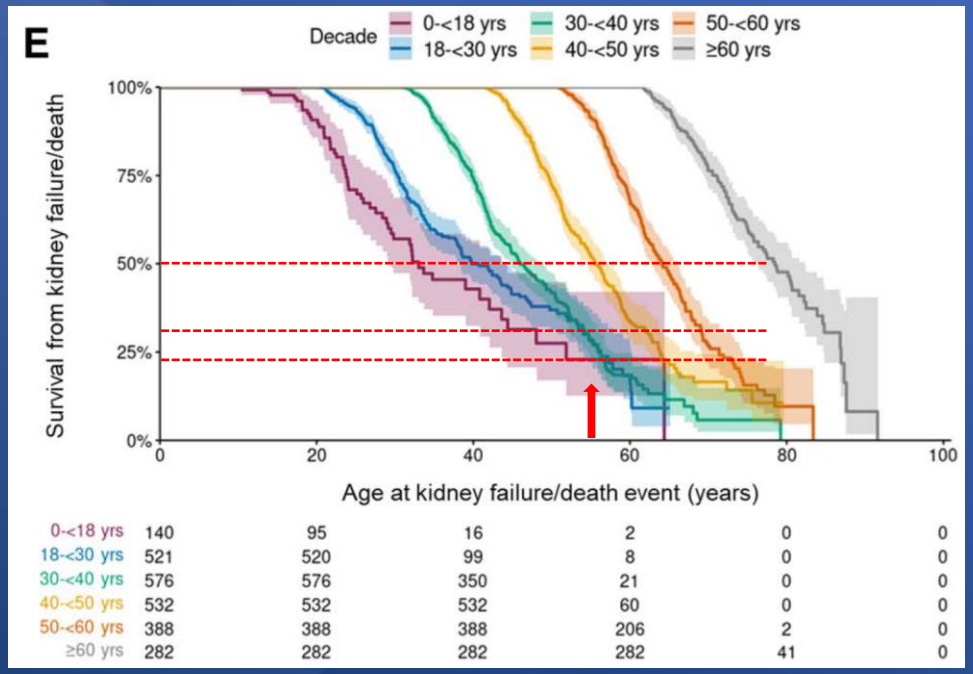
Conclusions Outcomes in this large IgA nephropathy cohort are generally poor with few patients expected to avoid kidney failure in their lifetime. Significantly, patients traditionally regarded as being low risk, with proteinuria <0.88 g/g (<100 mg/mmol), had high rates of kidney failure within 10 years.

CJASN 18: 727–738, 2023. doi: https://doi.org/10.2215/CJN.0000000000000135

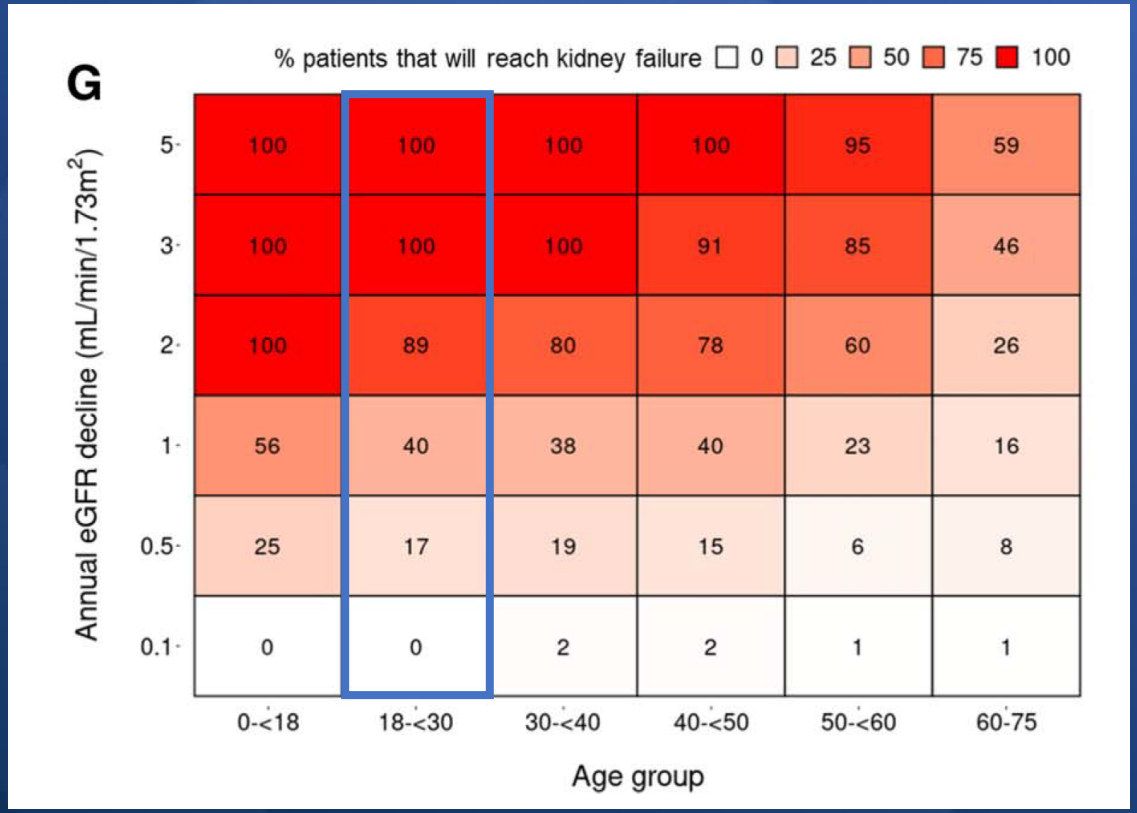
[1]UK Renal Registry, The UK Kidney Association, Bristol, United Kingdom
[2]Department of Renal Medicine, University College London, London, United Kingdom
[3]Travere Therapeutics, Inc., San Diego, California
[4]JAMCO Pharma Consulting, Stockholm, Sweden
[5]University of Bristol & Bristol Royal Hospital for Children, Bristol, United Kingdom
[6]University of Edinburgh, Edinburgh, United Kingdom
[7]University of Leicester & Leicester General Hospital, Leicester, United Kingdom

Correspondence: Dr. Jonathan Barratt, Department of Cardiovascular Sciences, University of Leicester, University





Pitcher D, et al. Clin J Am Soc Nephrol 2023



Pitcher D, et al. Clin J Am Soc Nephrol 2023

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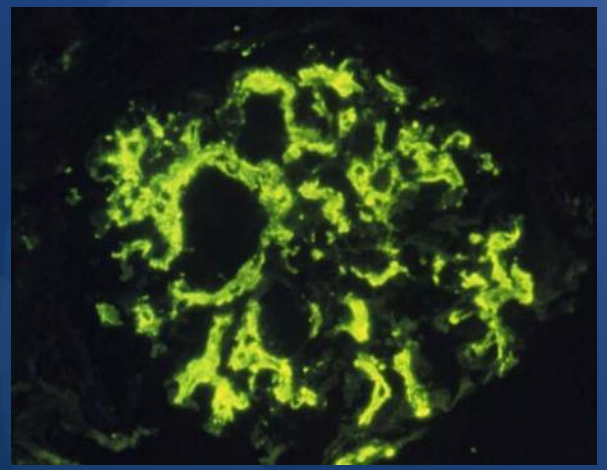
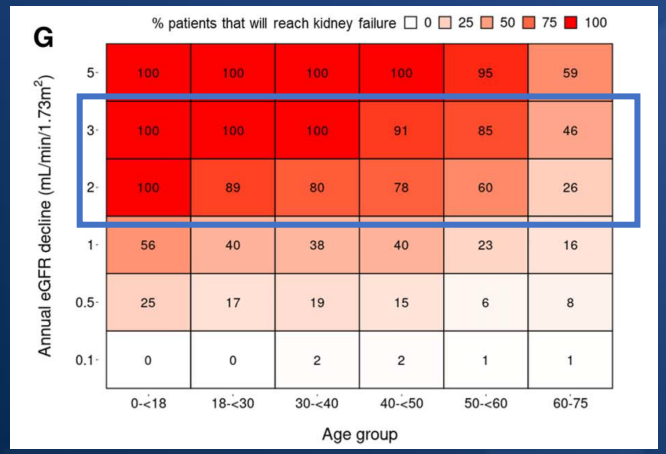
Leicester IgA Nephropathy Research Group





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Pitcher D, et al. Clin J Am Soc Nephrol 2023

clinical trial www.kidney-international.org

After ten years of follow-up, no difference between supportive care plus immunosuppression and supportive care alone in IgA nephropathy

see commentary on page 836

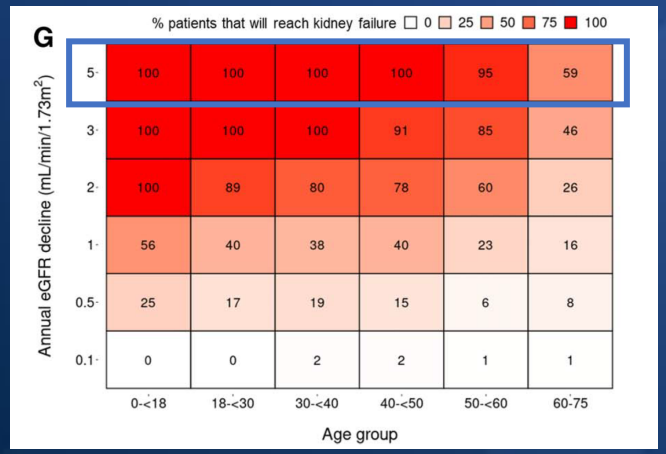
Thomas Rauen[1], Stephanie Wied[2], Christina Fitzner[2], Frank Eitner[1,3], Claudia Sommerer[4], Martin Zeier[4], Britta Otte[5], Ulf Panzer[6], Klemens Budde[7], Urs Benck[8], Peter R. Mertens[9], Uwe Kuhlmann[10], Oliver Witzke[11], Oliver Gross[12], Volker Vielhauer[13], Johannes F.E. Mann[14], Ralf-Dieter Hilgers[2] and Jürgen Floege[1]; for the STOP-IgAN Investigators[15]

Table 2 | Occurrence of secondary endpoints since randomization (based on the analysis of available cases at the end of the long-term observation)

	Supportive care			Supportive care plus immunosuppression					
Endpoints	Total	n (%)		Total	n (%)		Hazard ratio	95% Confidence interval	*P*
All-cause death	72	2 (2.8)		77	3 (3.9)		0.71	0.12–4.32	0.71
Onset of end-stage renal disease	72	17 (23.6)		77	20 (26.0)		0.90	0.47–1.73	0.74
GFR loss >40%[a]	70	28 (40.0)		73	20 (27.4)		1.62	0.91–2.89	0.10
GFR loss >30%[a]	70	38 (54.3)		73	29 (39.7)		1.28	0.78–2.08	0.33
	Total	Mean	SD	Total	Mean	SD			
Annual eGFR change since randomization (ml/min per 1.73 m^2)	80	−2.68	1.99	79	−2.36	2.19			0.46
Annual eGFR change after the randomized trial phase (ml/min per 1.73 m^2)	70	−3.15	2.44	71	−2.86	3.47			0.28
Protein-to-creatinine ratio at the end of observation (g/g)	30	1.29	1.34	33	1.28	2.49			0.99
Proteinuria at the end of observation (g/d)[b]	37	1.44	1.00	37	1.23	1.27			0.43

eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate.
[a]As compared with baseline eGFR.
[b]In some patients, proteinuria was available in g/g creatinine, whereas in others it was available in g/d.

Rauen T, et al. Kidney Int 2020



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Pitcher D, et al. Clin J Am Soc Nephrol 2023

Research

JAMA | Original Investigation

Effect of Oral Methylprednisolone on Decline in Kidney Function or Kidney Failure in Patients With IgA Nephropathy
The TESTING Randomized Clinical Trial

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Table 2. Primary and Secondary Outcomes in a Study of the Effect of Oral Methylprednisolone on Kidney Function Decline in Patients With IgA Nephropathy

Outcome	Methylprednisolone (n = 257)[a,b] No. of events	Methylprednisolone (n = 257)[a,b] Annual event rate (95% CI), %	Placebo (n = 246)[a,b] No. of events	Placebo (n = 246)[a,b] Annual event rate (95% CI), %	Rate difference (95% CI), %[b]	Hazard ratio (95% CI)[c]	*P* value[c]
Primary							
40% eGFR reduction, kidney failure, or death due to kidney disease[d,e]	74	7.3 (5.7 to 9.4)	106	12.1 (9.7 to 15.1)	−4.8 (−8.0 to −1.6)	0.53 (0.39 to 0.72)	<.001
Secondary							
30% eGFR reduction, kidney failure, or all-cause death	86	8.4 (6.7 to 10.6)	113	12.8 (10.3 to 15.8)	−4.4 (−7.7 to −1.0)	0.56 (0.42 to 0.75)	<.001
40% eGFR reduction, kidney failure, or all-cause death	78	7.7 (6.1 to 9.8)	106	12.2 (9.8 to 15.2)	−4.5 (−7.7 to −1.2)	0.56 (0.42 to 0.76)	<.001
50% eGFR reduction, kidney failure, or all-cause death	71	7.0 (5.5 to 9.1)	94	10.8 (8.6 to 13.7)	−3.8 (−6.9 to −0.7)	0.62 (0.46 to 0.85)	.003
Kidney failure requiring dialysis/transplant	50	4.9 (3.7 to 6.6)	67	7.8 (5.9 to 10.2)	−2.9 (−5.4 to −0.3)	0.59 (0.40 to 0.87)	.008
eGFR reduction							
30%	67	6.7 (5.2 to 8.7)	98	11.4 (9.1 to 14.3)	−4.7 (−7.8 to −1.6)	0.47 (0.34 to 0.65)	<.001
40%	57	5.8 (4.4 to 7.7)	91	10.9 (8.6 to 13.7)	−5.0 (−8.0 to −2.0)	0.44 (0.31 to 0.62)	<.001
50%	49	5.0 (3.7 to 6.7)	76	9.1 (7.0 to 11.7)	−4.1 (−6.8 to −1.3)	0.52 (0.36 to 0.74)	<.001
Death due to kidney failure[f]	1	0	1	0	0	NA	NA
Death due to any cause	6	0.5 (0.2 to 1.3)	3	0.3 (0.1 to 1.0)	0.2 (−0.4 to 0.8)	2.62 (0.53 to 13.05)	.24
Rate of eGFR decline, mL/min/1.73 m^2/y	Mean (95% CI)[g]				Mean difference (95% CI)[g]		*P* value[g]
Using all visits	−2.50 (−3.56 to −1.44)		−4.97 (−6.07 to −3.87)		2.46 (0.94 to 3.99)		.002
Excluding values from those receiving high-exposure treatment	−2.18 (−3.16 to −1.20)		−4.94 (−6.01 to −3.87)		2.76 (1.32 to 4.21)		<.001
Excluding values from those receiving treatment	−2.11 (−3.03 to −1.20)		−4.76 (−5.81 to −3.72)		2.65 (1.27 to 4.03)		<.001
Time-averaged proteinuria, g/d	1.70 (1.54 to 1.86)		2.39 (2.15 to 2.63)		−0.69 (−0.98 to −0.41)		<.001

[a] Median (IQR) follow-up was 3.5 (2.4-6.2) years.

[b] Yearly event rates (per 100 patients) and rate differences were obtained from a Poisson model adjusted for the stratification factors as fixed effects but without site as a random effect.

[c] Hazard ratios and corresponding *P* values were obtained from a Cox model adjusted for stratification factors as fixed effects and site as a random effect.

[d] Persistent ≥40% estimated glomerular filtration rate (eGFR) reduction was confirmed by a repeated reading at least 30 days later.

[e] Kidney failure requiring maintenance dialysis or kidney transplant.

[f] Too few events to derive CIs, estimates of effect, and *P* values.

[g] Means, mean differences, and corresponding *P* values were obtained from a linear model adjusted for stratification factors as fixed effects and site as a random effect. Yearly event rates (per 100 patients) and rate differences were obtained from a Poisson model adjusted for site as a random effect and proteinuria, eGFR, and kidney biopsy findings as fixed effects.

Lv J, et al. JAMA 2017

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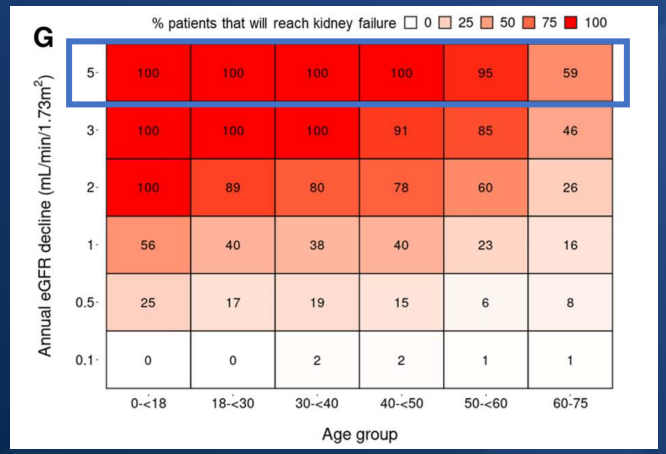

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Pitcher D, et al. Clin J Am Soc Nephrol 2023

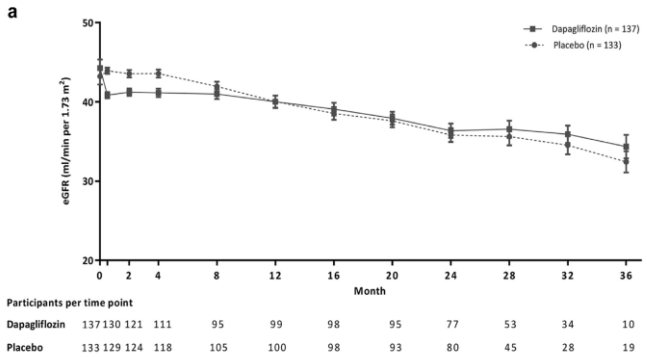
www.kidney-international.org clinical trial

A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy

see commentary on page 24

OPEN

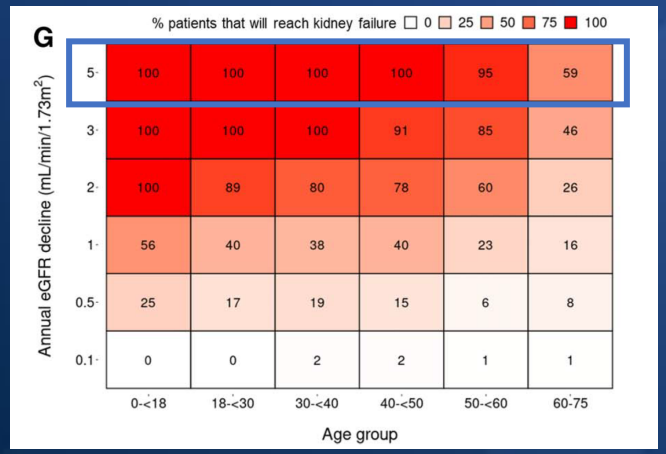
David C. Wheeler[1,2], Robert D. Toto[3], Bergur V. Stefánsson[4], Niels Jongs[5], Glenn M. Chertow[6,7], Tom Greene[8], Fan Fan Hou[9], John J.V. McMurray[10], Roberto Pecoits-Filho[11,12], Ricardo Correa-Rotter[13], Peter Rossing[14,15], C. David Sjöström[4], Kausik Umanath[16,17], Anna Maria Langkilde[4] and Hiddo J.L. Heerspink[5]; for the DAPA-CKD Trial Committees and Investigators



Effects of dapagliflozin on continuous outcomes

The least mean squares eGFR slopes from baseline to end of treatment in the dapagliflozin and placebo groups were −3.5 (SE, 0.5) and −4.7 (SE, 0.5) ml/min per 1.73 m^2 per year, respectively, resulting in a between-group difference of 1.2 ml/min per 1.73 m^2 per year (95% CI, −0.12 to 2.51 ml/min per 1.73 m^2 per year; Figure 4a). During the first 2 weeks, the eGFR reduction was larger in the dapagliflozin than placebo group (−3.4 [±0.4] vs. −0.5 [0.4] ml/min per 1.73 m^2). Thereafter, annual mean eGFR change was smaller with dapagliflozin compared with placebo (−2.2 [0.5] and −4.6 [0.47], respectively), resulting in a between-group difference of 2.4 ml/min per 1.73 m^2 per year (95% CI, 1.08–3.71 ml/min per 1.73 m^2 per year).

Wheeler DC, et al. Kidney Int 2021



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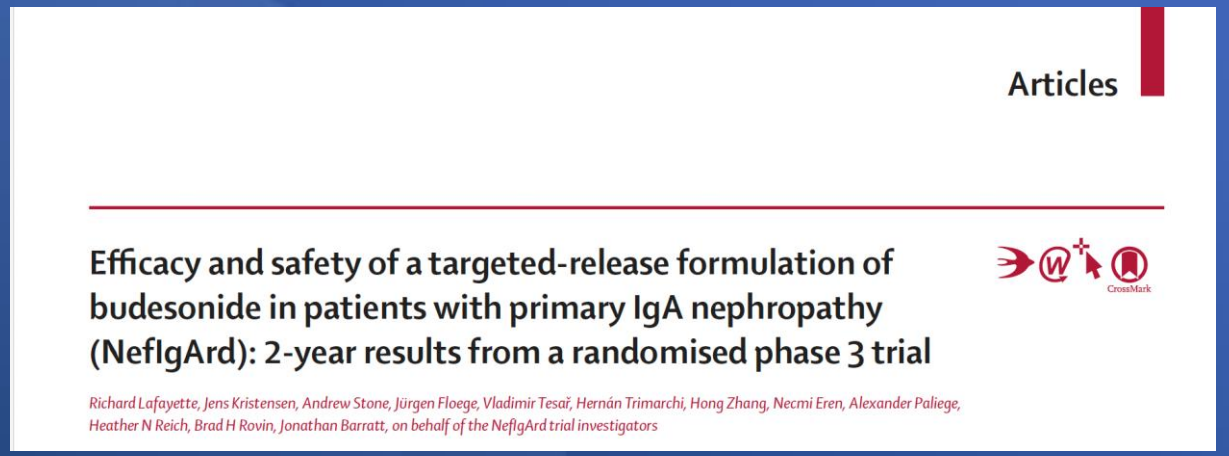
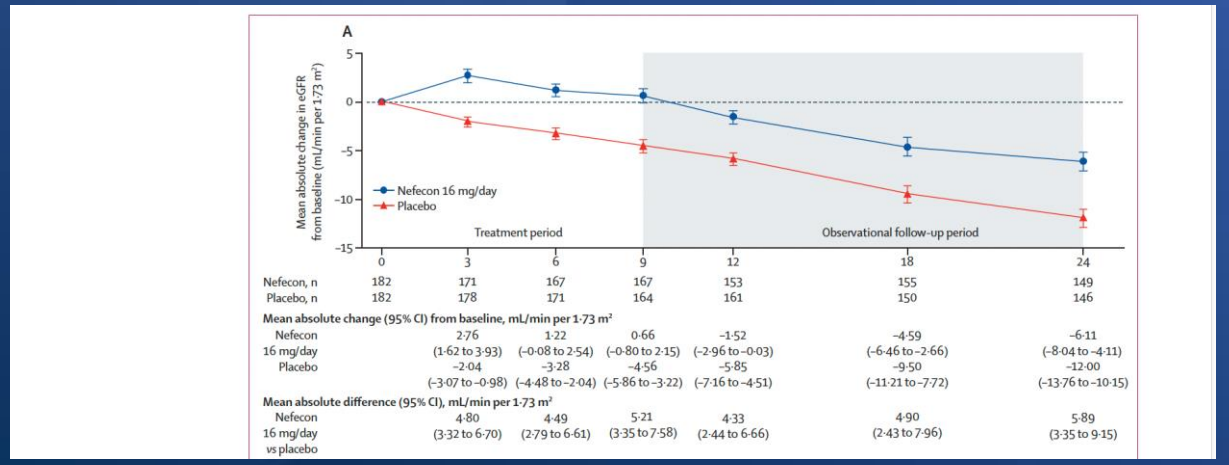
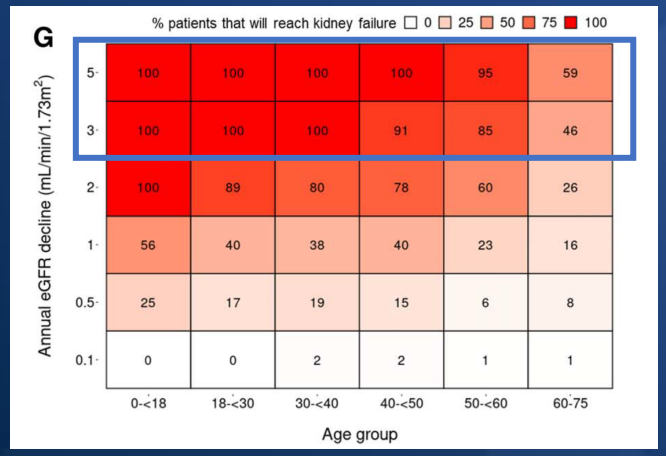
Pitcher D, et al. Clin J Am Soc Nephrol 2023





Lafayette R, et al. Lancet 2023



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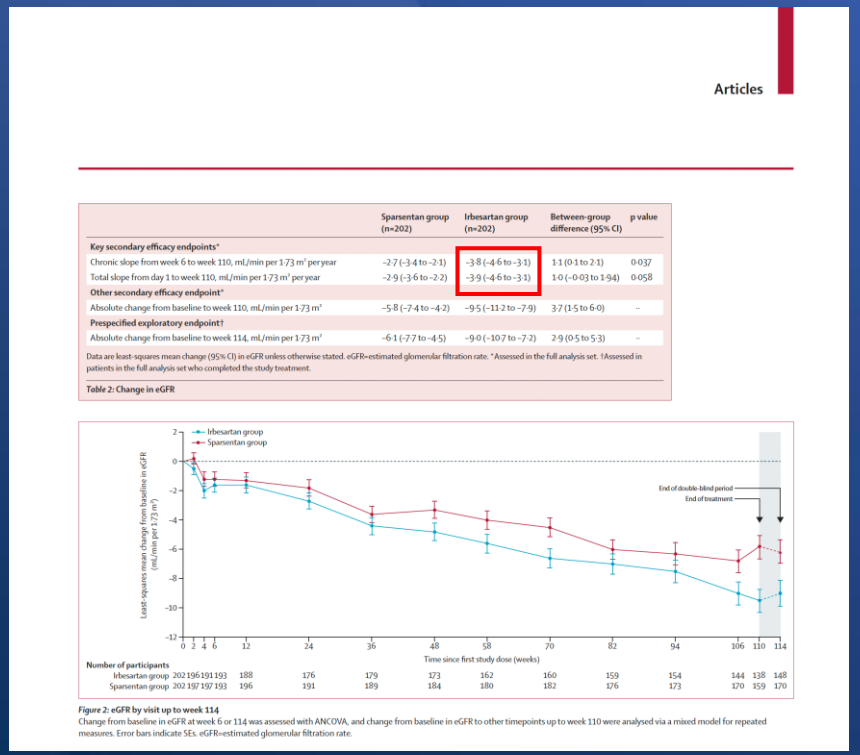
Pitcher D, et al. Clin J Am Soc Nephrol 2023


Articles

Efficacy and safety of sparsentan versus irbesartan in patients with IgA nephropathy (PROTECT): 2-year results from a randomised, active-controlled, phase 3 trial

Brad H Rovin*, Jonathan Barratt*, Hiddo J L Heerspink, Charles E Alpers, Stewart Bieler, Dong-Wan Chae, Ulysses A Diva, Jürgen Floege, Loreto Gesualdo, Jula K Inrig, Donald E Kohan, Radko Komers, Laura Ann Kooienga, Richard Lafayette, Bart Maes, Robert Małecki, Alex Mercer, Irene L Noronha, Se Won Oh, Chen Au Peh, Manuel Praga, Priscila Preciado, Jai Radhakrishnan, Michelle N Rheault, William E Rote, Sydney C W Tang, Vladimir Tesar, Howard Trachtman, Hernán Trimarchi, James A Tumlin, Muh Geot Wong, Vlado Perkovic, on behalf of the DUPRO steering committee and PROTECT Investigators†


Articles

	Sparsentan group (n=202)	Irbesartan group (n=202)	Between-group difference (95% CI)	p value
Key secondary efficacy endpoints*				
Chronic slope from week 6 to week 110, mL/min per 1·73 m² per year	−2·7 (−3·4 to −2·1)	−3·8 (−4·6 to −3·1)	1·1 (0·1 to 2·1)	0·037
Total slope from day 1 to week 110, mL/min per 1·73 m² per year	−2·9 (−3·6 to −2·2)	−3·9 (−4·6 to −3·1)	1·0 (−0·03 to 1·94)	0·058
Other secondary efficacy endpoint*				
Absolute change from baseline to week 110, mL/min per 1·73 m²	−5·8 (−7·4 to −4·2)	−9·5 (−11·2 to −7·9)	3·7 (1·5 to 6·0)	..
Prespecified exploratory endpoint†				
Absolute change from baseline to week 114, mL/min per 1·73 m²	−6·1 (−7·7 to −4·5)	−9·0 (−10·7 to −7·2)	2·9 (0·5 to 5·3)	..

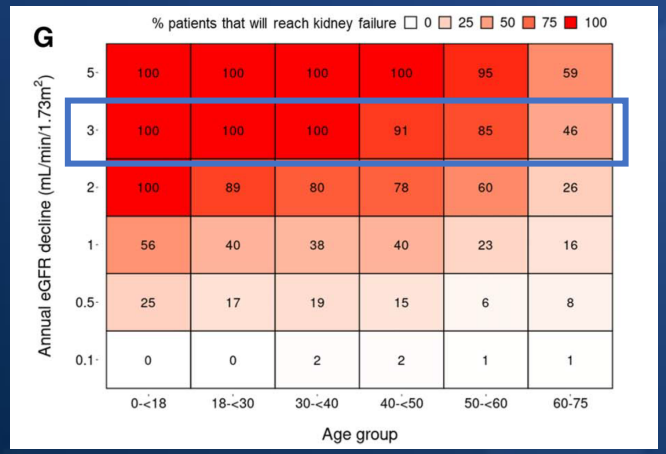
Data are least-squares mean change (95% CI) in eGFR unless otherwise stated. eGFR=estimated glomerular filtration rate. *Assessed in the full analysis set. †Assessed in patients in the full analysis set who completed the study treatment.

Table 2: Change in eGFR

Figure 2: eGFR by visit up to week 114

Change from baseline in eGFR at week 6 or 114 was assessed with ANCOVA, and change from baseline in eGFR to other timepoints up to week 110 were analysed via a mixed model for repeated measures. Error bars indicate SEs. eGFR=estimated glomerular filtration rate.

Rovin BH, et al. Lancet 2023



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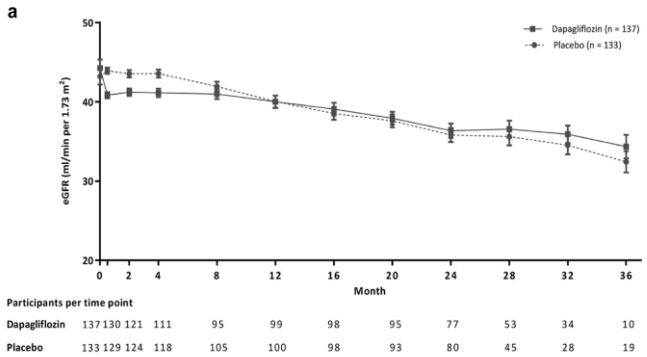

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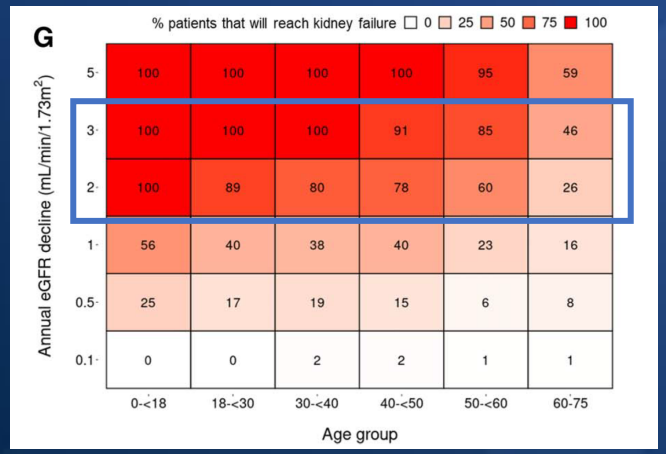

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	Total	Mean	SD	Total	Mean	SD			
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Annual eGFR change after the randomized trial phase (ml/min per 1.73 m^2)	70	−3.15	2.44	71	−2.86	3.47			0.28
Protein-to-creatinine ratio at the end of observation (g/g)	30	1.29	1.34	33	1.28	2.49			0.99
Proteinuria at the end of observation (g/d)[b]	37	1.44	1.00	37	1.23	1.27			0.43

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Rauen T, et al. Kidney Int 2020

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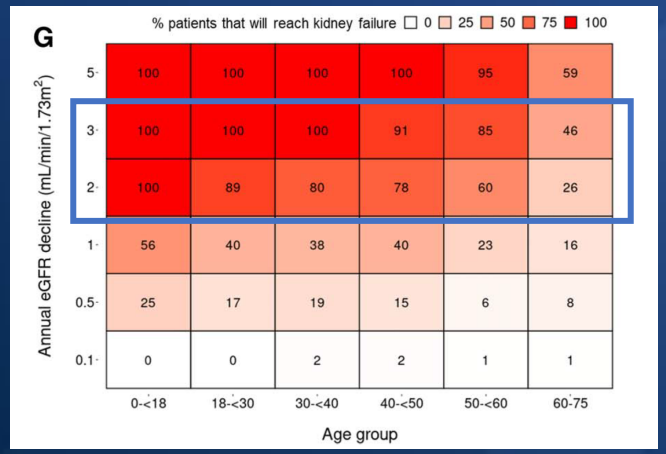

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Outcome	Methylprednisolone (n = 257)[a,b] No. of events	Methylprednisolone (n = 257)[a,b] Annual event rate (95% CI), %	Placebo (n = 246)[a,b] No. of events	Placebo (n = 246)[a,b] Annual event rate (95% CI), %	Rate difference (95% CI), %[b]	Hazard ratio (95% CI)[c]	P value[c]
Primary							
40% eGFR reduction, kidney failure, or death due to kidney disease[d,e]	74	7.3 (5.7 to 9.4)	106	12.1 (9.7 to 15.1)	−4.8 (−8.0 to −1.6)	0.53 (0.39 to 0.72)	<.001
Secondary							
30% eGFR reduction, kidney failure, or all-cause death	86	8.4 (6.7 to 10.6)	113	12.8 (10.3 to 15.8)	−4.4 (−7.7 to −1.0)	0.56 (0.42 to 0.75)	<.001
40% eGFR reduction, kidney failure, or all-cause death	78	7.7 (6.1 to 9.8)	106	12.2 (9.8 to 15.2)	−4.5 (−7.7 to −1.2)	0.56 (0.42 to 0.76)	<.001
50% eGFR reduction, kidney failure, or all-cause death	71	7.0 (5.5 to 9.1)	94	10.8 (8.6 to 13.7)	−3.8 (−6.9 to −0.7)	0.62 (0.46 to 0.85)	.003
Kidney failure requiring dialysis/transplant	50	4.9 (3.7 to 6.6)	67	7.8 (5.9 to 10.2)	−2.9 (−5.4 to −0.3)	0.59 (0.40 to 0.87)	.008
eGFR reduction							
30%	67	6.7 (5.2 to 8.7)	98	11.4 (9.1 to 14.3)	−4.7 (−7.8 to −1.6)	0.47 (0.34 to 0.65)	<.001
40%	57	5.8 (4.4 to 7.7)	91	10.9 (8.6 to 13.7)	−5.0 (−8.0 to −2.0)	0.44 (0.31 to 0.62)	<.001
50%	49	5.0 (3.7 to 6.7)	76	9.1 (7.0 to 11.7)	−4.1 (−6.8 to −1.3)	0.52 (0.36 to 0.74)	<.001
Death due to kidney failure[f]	1	0	1	0	0	NA	NA
Death due to any cause	6	0.5 (0.2 to 1.3)	3	0.3 (0.1 to 1.0)	0.2 (−0.4 to 0.8)	2.62 (0.53 to 13.05)	.24
Rate of eGFR decline, mL/min/1.73 m^2/y	Mean (95% CI)[g]				Mean difference (95% CI)[g]		P value[g]
Using all visits	−2.50 (−3.56 to −1.44)		−4.97 (−6.07 to −3.87)		2.46 (0.94 to 3.99)		.002
Excluding values from those receiving high-exposure treatment	−2.18 (−3.16 to −1.20)		−4.94 (−6.01 to −3.87)		2.76 (1.32 to 4.21)		<.001
Excluding values from those receiving treatment	−2.11 (−3.03 to −1.20)		−4.76 (−5.81 to −3.72)		2.65 (1.27 to 4.03)		<.001
Time-averaged proteinuria, g/d	1.70 (1.54 to 1.86)		2.39 (2.15 to 2.63)		−0.69 (−0.98 to −0.41)		<.001

[a] Median (IQR) follow-up was 3.5 (2.4-6.2) years.

[b] Yearly event rates (per 100 patients) and rate differences were obtained from a Poisson model adjusted for the stratification factors as fixed effects but without site as a random effect.

[c] Hazard ratios and corresponding *P* values were obtained from a Cox model adjusted for stratification factors as fixed effects and site as a random effect.

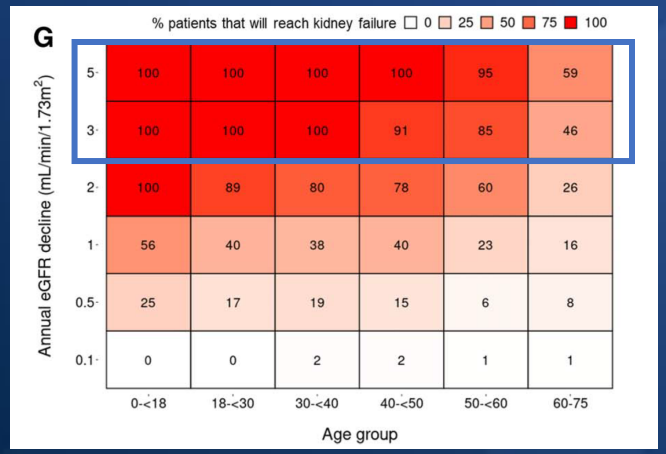
[d] Persistent ≥40% estimated glomerular filtration rate (eGFR) reduction was confirmed by a repeated reading at least 30 days later.

[e] Kidney failure requiring maintenance dialysis or kidney transplant.

[f] Too few events to derive CIs, estimates of effect, and *P* values.

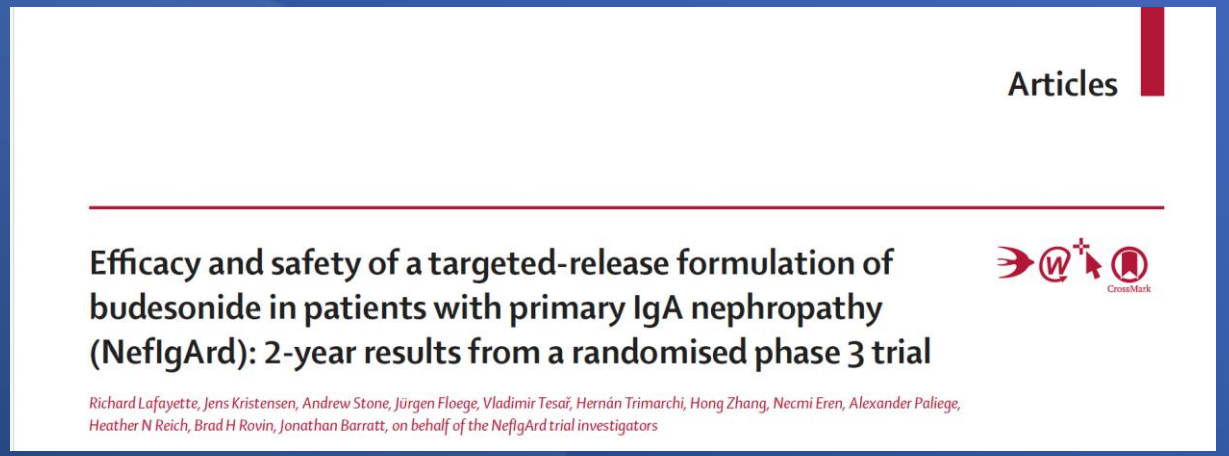
[g] Means, mean differences, and corresponding *P* values were obtained from a linear model adjusted for stratification factors as fixed effects and site as a random effect. Yearly event rates (per 100 patients) and rate differences were obtained from a Poisson model adjusted for site as a random effect and proteinuria, eGFR, and kidney biopsy findings as fixed effects.

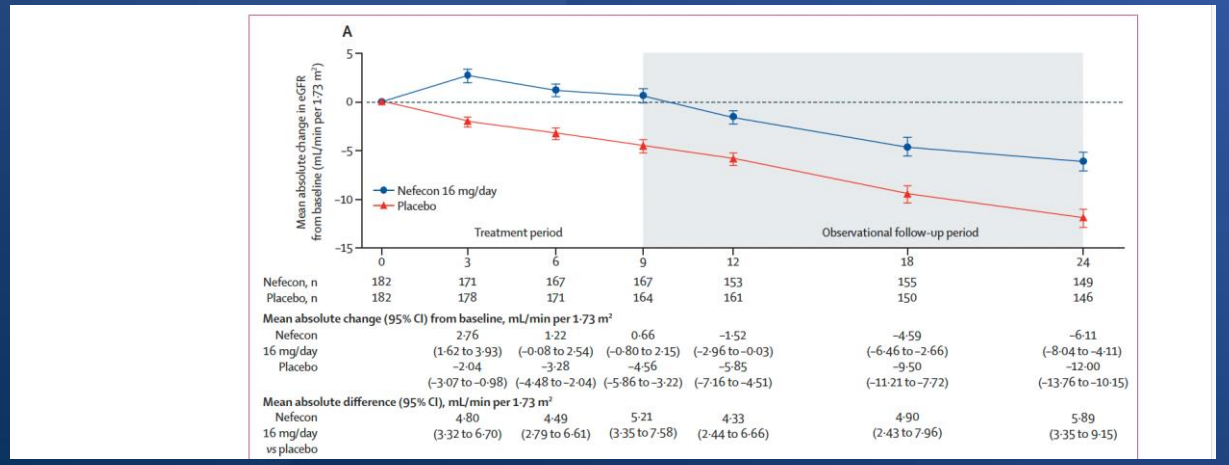
Lv J, et al. JAMA 2017



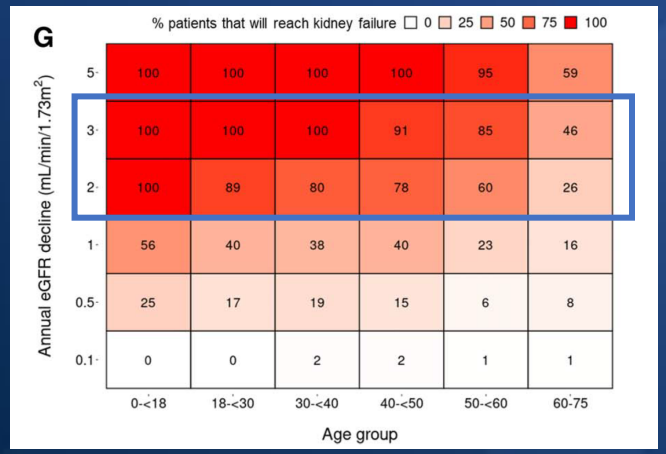
This retrospective cohort study used data from the RaDaR IgA nephropathy cohort, for which enrollment began in 2013. Patients eligible for enrollment must have a biopsy-proven diagnosis of IgA nephropathy plus proteinuria >0.5 g/day or eGFR <60 mL/min/1.73m^2 at any time in the history of their disease. All forms of secondary IgA nephropathy are excluded. Further description of the data source is included in the **Supplemental Methods**.

Pitcher D, et al. Clin J Am Soc Nephrol 2023





Lafayette R, et al. Lancet 2023



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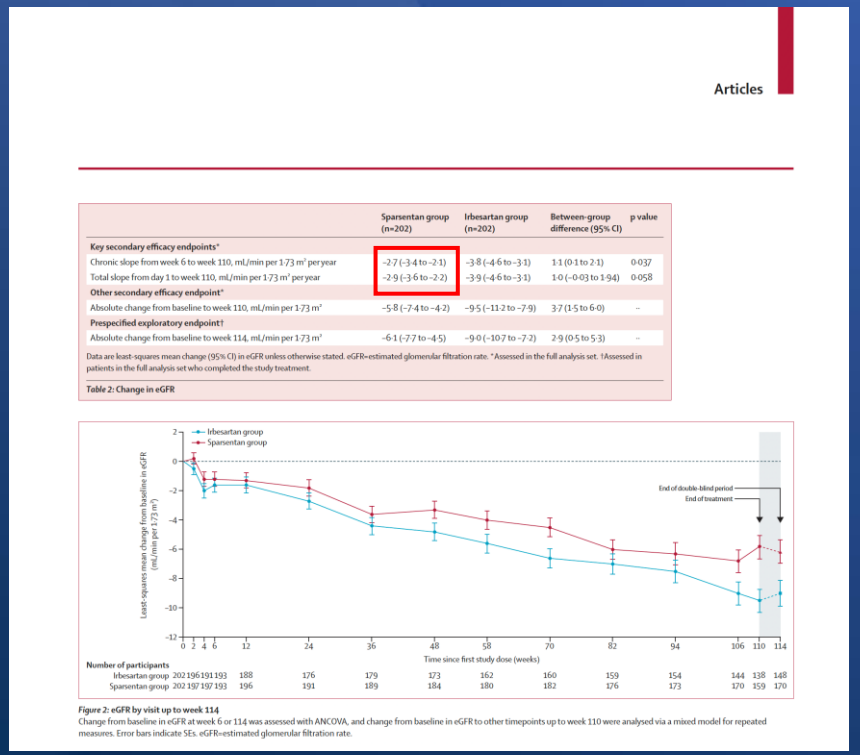
Articles

Efficacy and safety of sparsentan versus irbesartan in patients with IgA nephropathy (PROTECT): 2-year results from a randomised, active-controlled, phase 3 trial

Brad H Rovin*, Jonathan Barratt*, Hiddo J L Heerspink, Charles E Alpers, Stewart Bieler, Dong-Wan Chae, Ulysses A Diva, Jürgen Floege, Loreto Gesualdo, Jula K Inrig, Donald E Kohan, Radko Komers, Laura Ann Kooienga, Richard Lafayette, Bart Maes, Robert Małecki, Alex Mercer, Irene L Noronha, Se Won Oh, Chen Au Peh, Manuel Praga, Priscila Preciado, Jai Radhakrishnan, Michelle N Rheault, William E Rote, Sydney C W Tang, Vladimir Tesar, Howard Trachtman, Hernán Trimarchi, James A Tumlin, Muh Geot Wong, Vlado Perkovic, on behalf of the DUPRO steering committee and PROTECT Investigators†


Articles

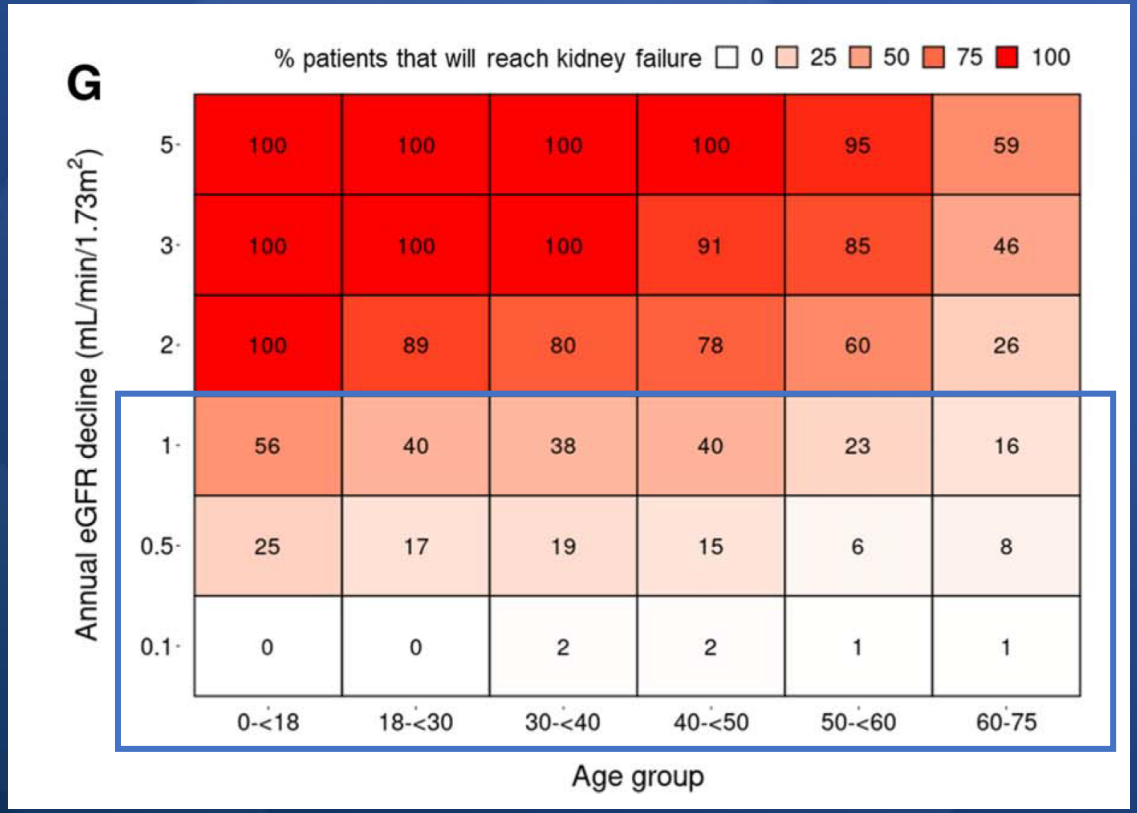
	Sparsentan group (n=202)	Irbesartan group (n=202)	Between-group difference (95% CI)	p value
Key secondary efficacy endpoints*				
Chronic slope from week 6 to week 110, mL/min per 1·73 m² per year	−2·7 (−3·4 to −2·1)	−3·8 (−4·6 to −3·1)	1·1 (0·1 to 2·1)	0·037
Total slope from day 1 to week 110, mL/min per 1·73 m² per year	−2·9 (−3·6 to −2·2)	−3·9 (−4·6 to −3·1)	1·0 (−0·03 to 1·94)	0·058
Other secondary efficacy endpoint*				
Absolute change from baseline to week 110, mL/min per 1·73 m²	−5·8 (−7·4 to −4·2)	−9·5 (−11·2 to −7·9)	3·7 (1·5 to 6·0)	..
Prespecified exploratory endpoint†				
Absolute change from baseline to week 114, mL/min per 1·73 m²	−6·1 (−7·7 to −4·5)	−9·0 (−10·7 to −7·2)	2·9 (0·5 to 5·3)	..

Data are least-squares mean change (95% CI) in eGFR unless otherwise stated. eGFR=estimated glomerular filtration rate. *Assessed in the full analysis set. †Assessed in patients in the full analysis set who completed the study treatment.

Table 2: Change in eGFR

Figure 2: eGFR by visit up to week 114
Change from baseline in eGFR at week 6 or 114 was assessed with ANCOVA, and change from baseline in eGFR to other timepoints up to week 110 were analysed via a mixed model for repeated measures. Error bars indicate SEs. eGFR=estimated glomerular filtration rate.

Rovin BH, et al. Lancet 2023



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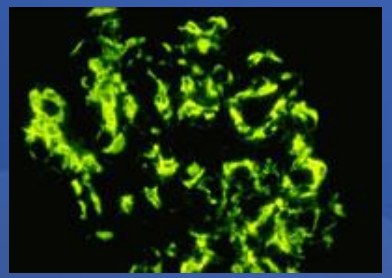


early **Disease natural history** *late*

Relative contribution to nephron loss

Disease-specific Immune mediated nephron loss

"Treating "autoimmunity"

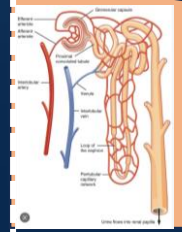
Generic response to loss of nephrons, hypertension

&

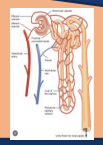
tubulointerstitial response to proteinuria

causing further nephron loss

"Treating CKD"



Nephron number



Therapeutic window to address drivers of nephron loss

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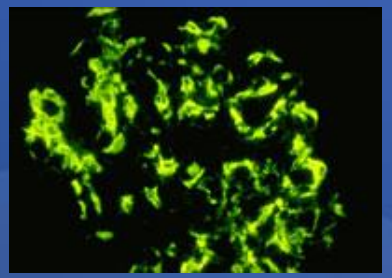

early — Disease natural history — late

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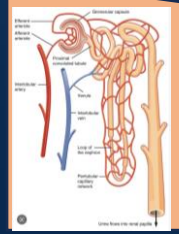

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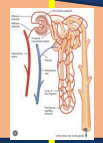
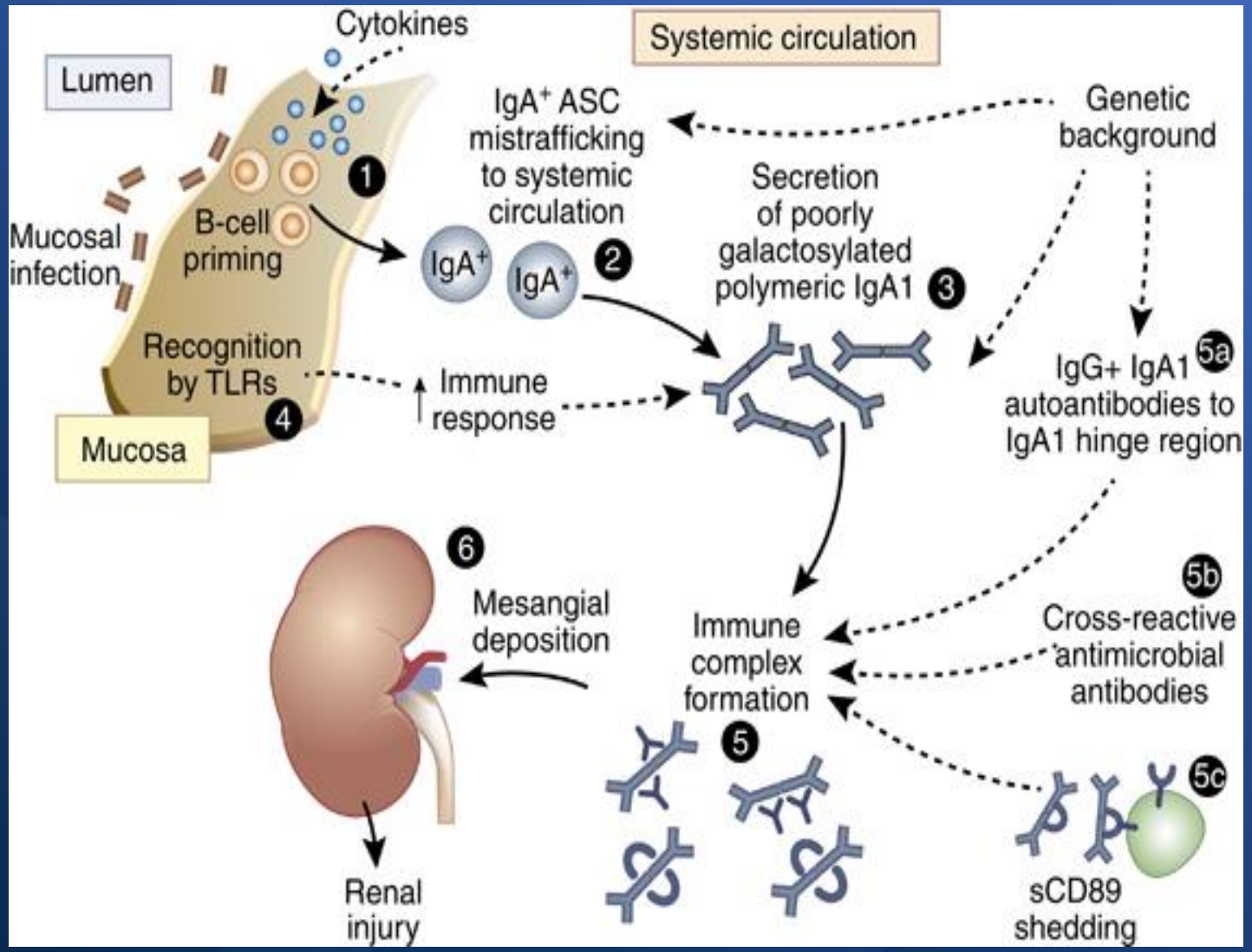


Typical time point IgAN is diagnosed

Therapeutic window to address drivers of nephron loss



Boyd JK, et al. Kidney Int 2012

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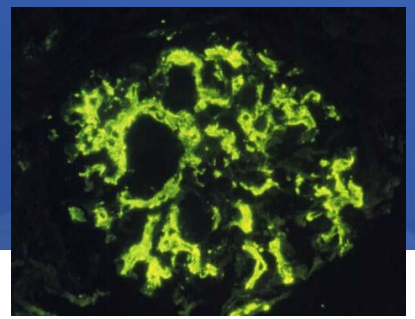

IgA1-containing immune complexes

Mesangial IgA1-immune complex deposition

Filtration of IgA1-immune complexes into urine

Release of pro-inflammatory and pro-fibrotic mediators

Glomerulo-podocytic crosstalk

Glomerulo-tubular crosstalk

Mesangial cell proliferation **(M)**

Inflammatory cell recruitment into glomeruli **(E)**

Uncontrolled inflammatory response **(C)**

Podocyte injury & glomerulosclerosis **(S)**

PTEC activation & tubulointerstitial fibrosis **(T)**

COMPLEMENT ACTIVATION

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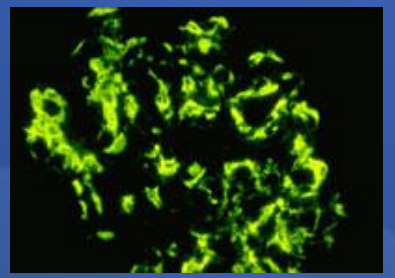

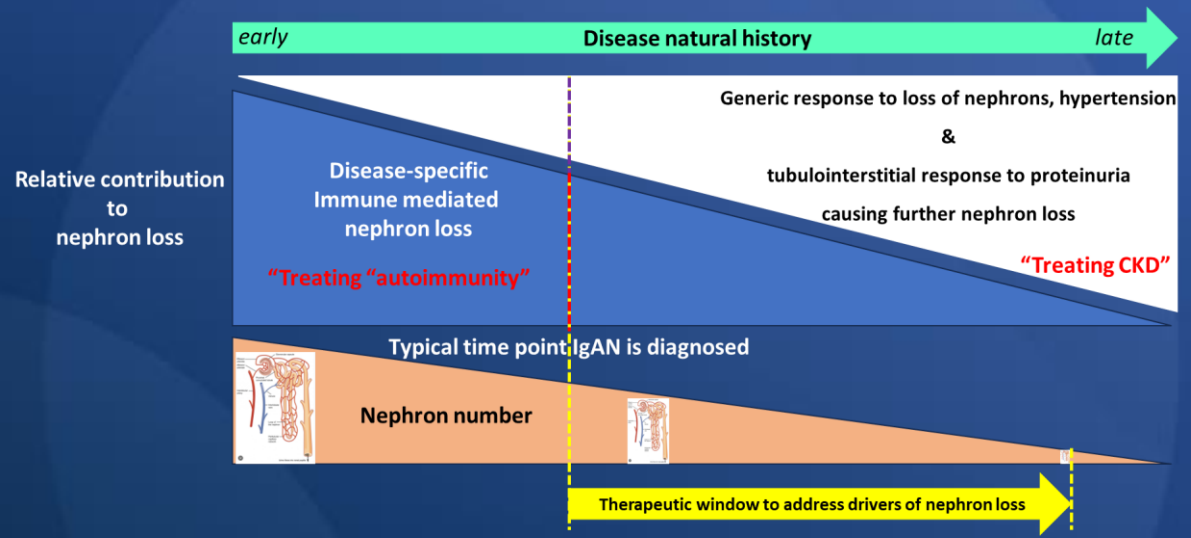

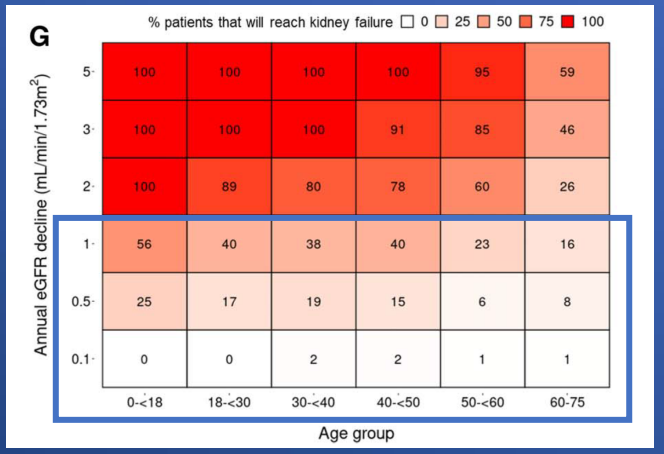

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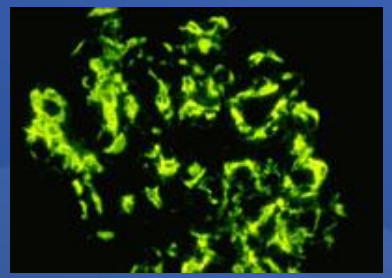

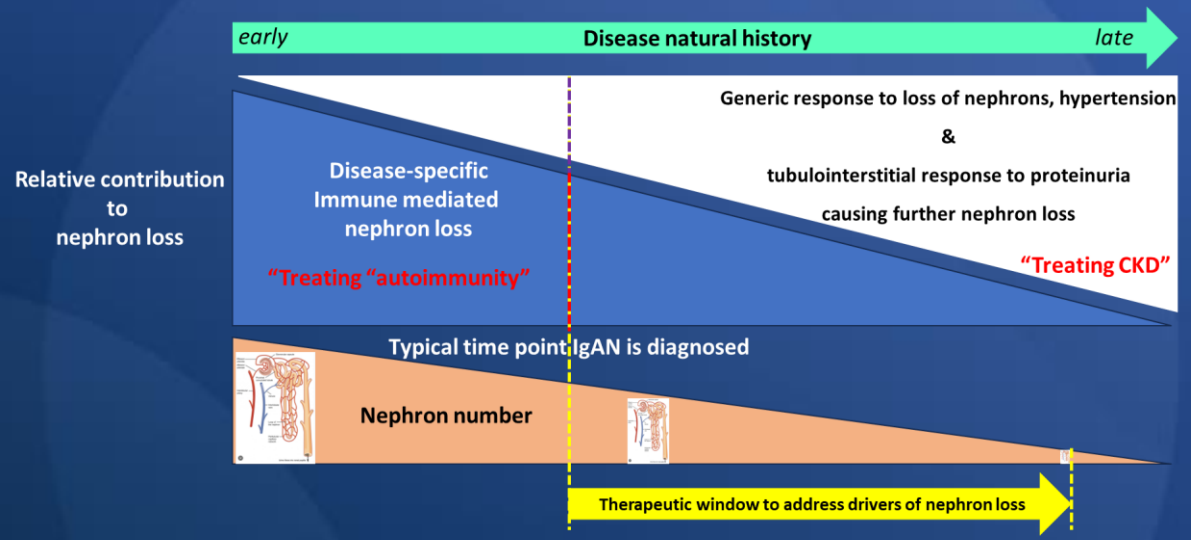

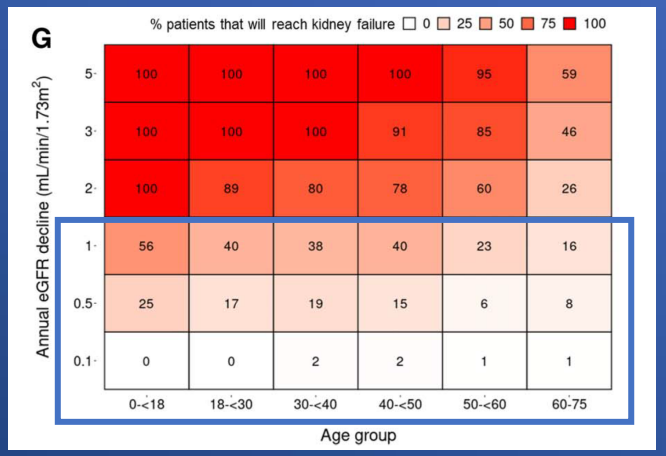

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RASi | SGLT2i | Optimised supportive kidney care | ERA | MRA

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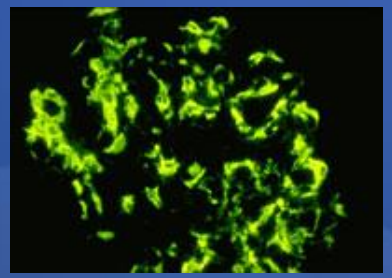

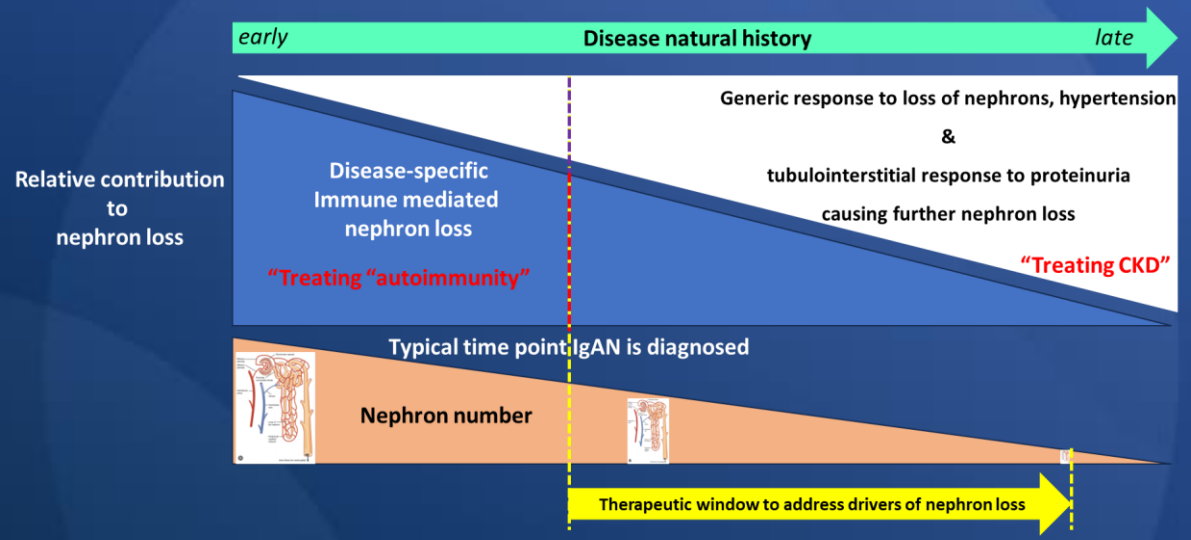

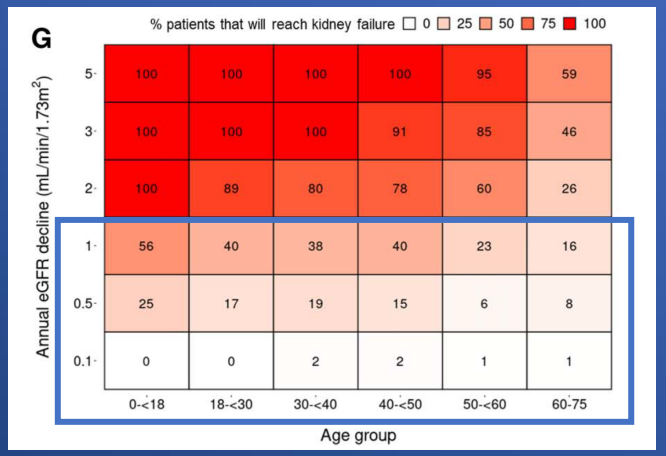

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"Target the IgA-induced kidney damage-autoimmunity"

Optimised supportive kidney care

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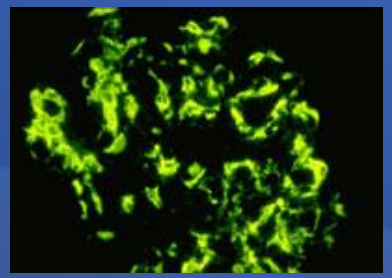

Inflammation

Pathogenic IgA Synthesis

Fibrosis

“Target the IgA-induced kidney damage-autoimmunity”

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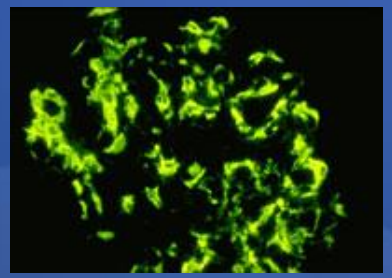

Fibrosis

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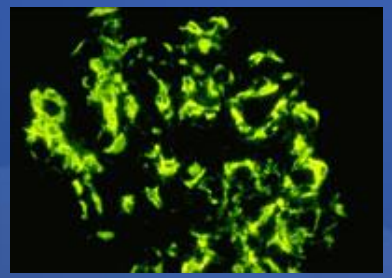

Inflammation

Glucocorticosteroids

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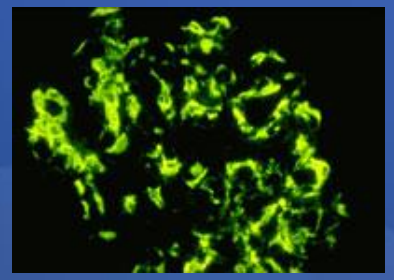


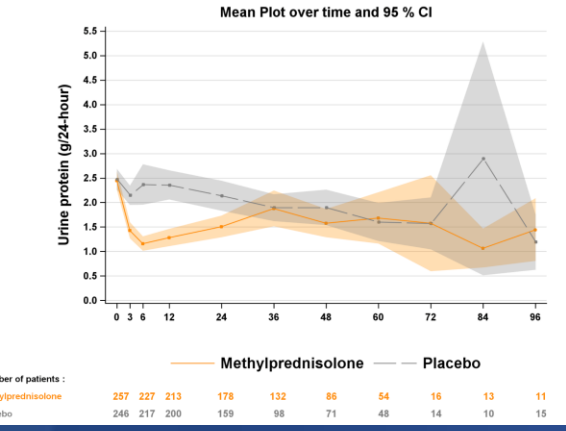
Research

JAMA | Original Investigation

Effect of Oral Methylprednisolone on Decline in Kidney Function or Kidney Failure in Patients With IgA Nephropathy
The TESTING Randomized Clinical Trial

Jicheng Lv, MD; Muh Geot Wong, PhD; Michelle A. Hladunewich, MD; Vivekanand Jha, MD; Lai Seong Hooi, MB, BChir; Helen Monaghan, BSc; Minghui Zhao, MD; Sean Barbour, MD, PhD; Meg J. Jardine, PhD; Heather N. Reich, MD; Daniel Cattran, MD; Richard Glassock, MD; Adeera Levin, MD; David C. Wheeler, MD; Mark Woodward, PhD; Laurent Billot, MSc, MRes; Sandrine Stepien, MSc; Kris Rogers, PhD; Tak Mao Chan, MD; Zhi-Hong Liu, MD; David W. Johnson, MBBS, PhD; Alan Cass, PhD; John Feehally, MD; Jürgen Floege, MD; Giuseppe Remuzzi, MD; Yangfeng Wu, MD; Rajiv Agarwal, MD; Hong Zhang, MD, PhD; Vlado Perkovic, MBBS, PhD; for the TESTING Study Group

A) Mean 24 hour protein excretion by randomized group over time



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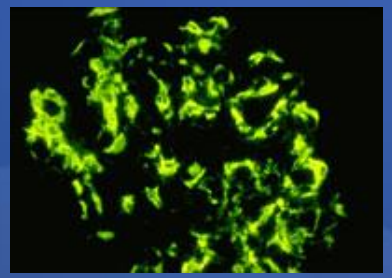

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eTable 4 (modified): Serious Adverse events randomized by group overall

	Methylprednisolone (N = 257)	Placebo (N = 246)	
Number of SAE	37	8	*
Number of patients with atleast one SAE (%)			
Hospitalization/prolonged hospitalization	28 (11)	7 (2)	*
Resulted in death	4 (2)	0 (0)	*
Life-threatening	4 (2)	0 ()	*
Important medical event	2 (0.8)	0 ()	
Persistent/significant disability/incapacity	1 (0.4)	0 (0)	
Number of patients reporting the following SAE of special interest per protocol			
Severe infection requiring hospitalization	17 (7)	2 (1)	
Pneumocystis Jirovecii pneumonia	4 (2)	0 (0)	
Pneumonia or respiratory tract infection	3 (1)	0 (0)	
Sepsis	2 (0.8)	1 (0.4)	
Urinary tract infection	2 (0.8)	0 (0)	
Multiple skin infection	1 (0.4)	0 (0)	
Nocardia infection	1 (0.4)	0 (0)	
Cryptococcal meningitis	1 (0.4)	0 (0)	
Tuberculosis with bacterial infection	1 (0.4)	0 (0)	
Perianal abscess	1 (0.4)	0 (0)	
Acute febrile illness	0 (0)	1 (0.4)	
Other	1 (0.4)	1 (0.4)	
Gastrointestinal bleeding requiring hospitalization	3 (1)	1 (0.4)	
Clinical evidence fractures or osteoporosis	3 (1)	0 (0)	*
New onset diabetes mellitus	2 (0.8)	0 (0)	*

Lv J, et al. JAMA 2017

Inflammation

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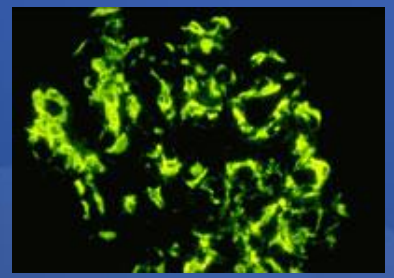
Leicester IgA Nephropathy Research Group



Research

JAMA | Original Investigation

Effect of Oral Methylprednisolone on Decline in Kidney Function or Kidney Failure in Patients With IgA Nephropathy
The TESTING Randomized Clinical Trial

Jicheng Lv, MD; Muh Geot Wong, PhD; Michelle A. Hladunewich, MD; Vivekanand Jha, MD; Lai Seong Hooi, MB, BChir; Helen Monaghan, BSc; Minghui Zhao, MD; Sean Barbour, MD, PhD; Meg J. Jardine, PhD; Heather N. Reich, MD; Daniel Cattran, MD; Richard Glassock, MD; Adeera Levin, MD; David C. Wheeler, MD; Mark Woodward, PhD; Laurent Billot, MSc, MRes; Sandrine Stepien, MSc; Kris Rogers, PhD; Tak Mao Chan, MD; Zhi-Hong Liu, MD; David W. Johnson, MBBS, PhD; Alan Cass, PhD; John Feehally, MD; Jürgen Floege, MD; Giuseppe Remuzzi, MD; Yangfeng Wu, MD; Rajiv Agarwal, MD; Hong Zhang, MD, PhD; Vlado Perkovic, MBBS, PhD; for the TESTING Study Group

Lv J, et al. JAMA 2017

CUH Ospidéil Ollscoile Chorcaí Cork University Hospitals

Mood Changes Associated with High-Dose Corticosteroids in Adults with Glomerular Disease

UCC Coláiste na hOllscoile Corcaigh University College Cork, Ireland

Authors: Fergus Daly[1], Daniel Brady[1], Darren Dahly[2], Michelle M. O'Shaughnessy[3], Sarah M. Moran[1]. Dept. of Renal Medicine, Cork University Hospital, [2] Clinical Research Facility, University College Cork, [3] Dept. of Nephrology, University Hospital Galway.

Background

Glomerulonephritis (GN) can be caused by a variety of underlying conditions, many of which are treated with high dose corticosteroids. There is a paucity of knowledge regarding the frequency, severity, and predictors of neuropsychiatric toxicity from high-dose corticosteroids in adults with glomerular diseases.

Methods

We conducted a prospective, survey-based study of adults with newly diagnosed or relapsing biopsy-proven minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), IgA nephropathy (IgAN), and membranous nephropathy (MN). Institutional ethical approval was granted.

Three identical questionnaires were provided for self-completion at enrolment, 2- & 12-weeks post-enrolment. The questionnaire was adapted from two existing surveys, developed and validated to measure mania (Altman Self-Rating Mania Scale) and depression (Patient Health

Results

30 patients were enrolled. Biopsy diagnoses included: MN (10), MCD (9), FSGS (4) and IgAN (7). 60% (18) were new diagnoses. 43% (13) had a prior psychiatric diagnosis (depression (8), anxiety (4), post traumatic stress disorder (1)) The median age was 54 years. There was no significant difference between groups in proteinuria or GFR at baseline level, however serum albumin was lower in the steroid treated group (25g/L vs 32g/L). 47% (14) of participants received corticosteroids, while the remainder(non-exposed: n=16) received no form of immunosuppressive therapy during their 12-weeks of enrolment.

Mania: ASRM scores at 2-weeks were significantly higher in the corticosteroid-exposed group compared to the immunosuppressant-naive control group ($p < 0.001$). Patients treated with corticosteroids experienced a mean ASRM score increase from baseline of 9 (standard deviation = 4.2) at 2-weeks, whereas their non-exposed counterparts experienced a negligible change.

Depression: A significant between-group difference in PHQ-9 (depression) scores at 12-weeks was observed with the corticosteroid group recording

Daly F, et al. ASN Kidney Week 2023, TH-PO588.

Inflammation

Glucocorticosteroids

"Target the IgA-induced kidney damage-autoimmunity"

Optimised supportive kidney care

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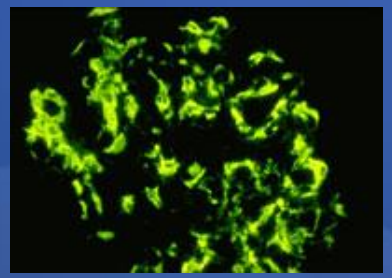
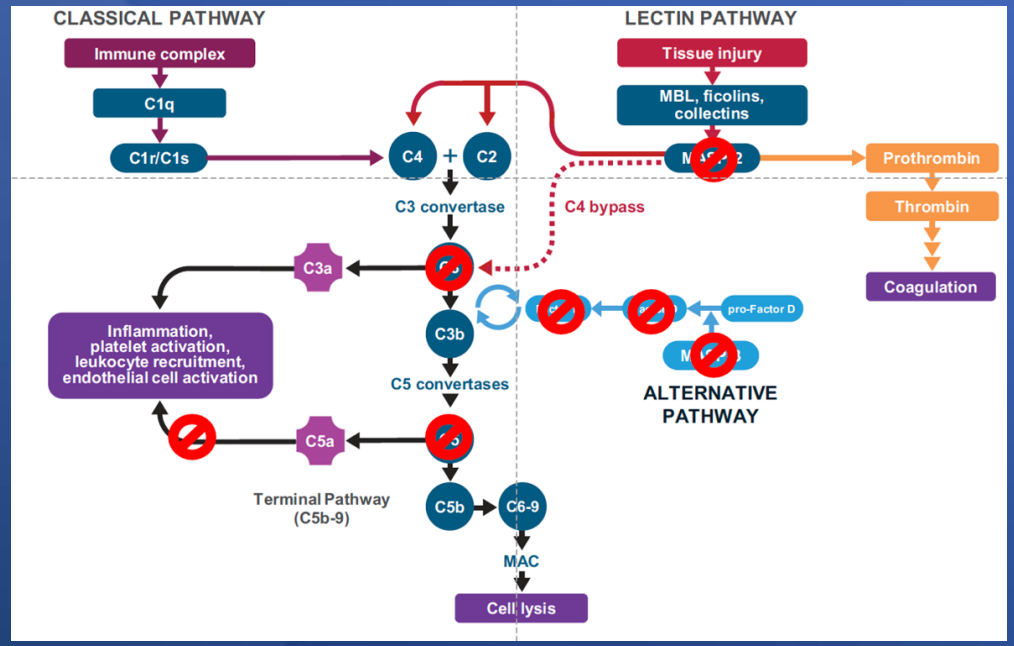


Inflammation



Complement inhibitors

“Target the IgA-induced kidney damage-autoimmunity”

Optimised supportive kidney care

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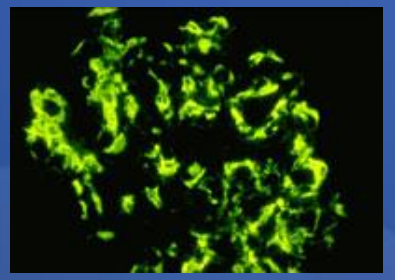
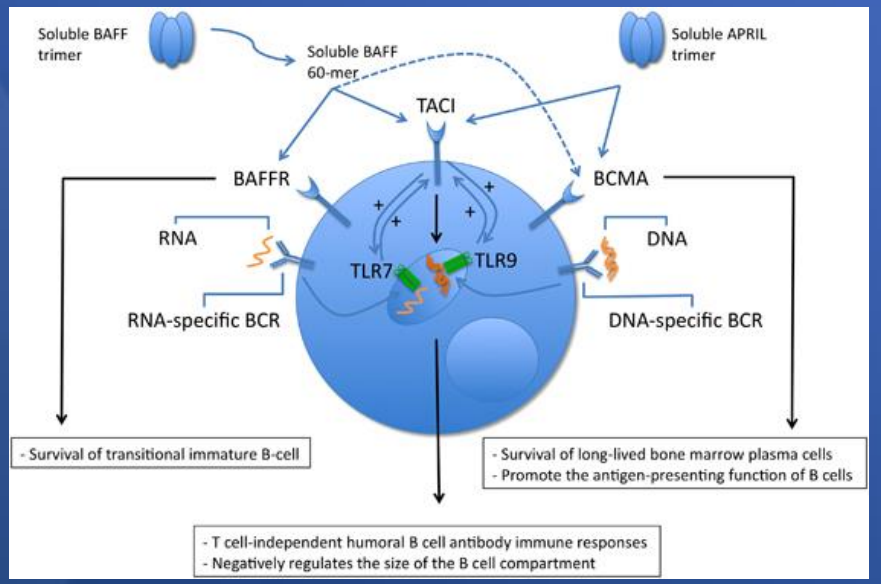


Pathogenic IgA Synthesis

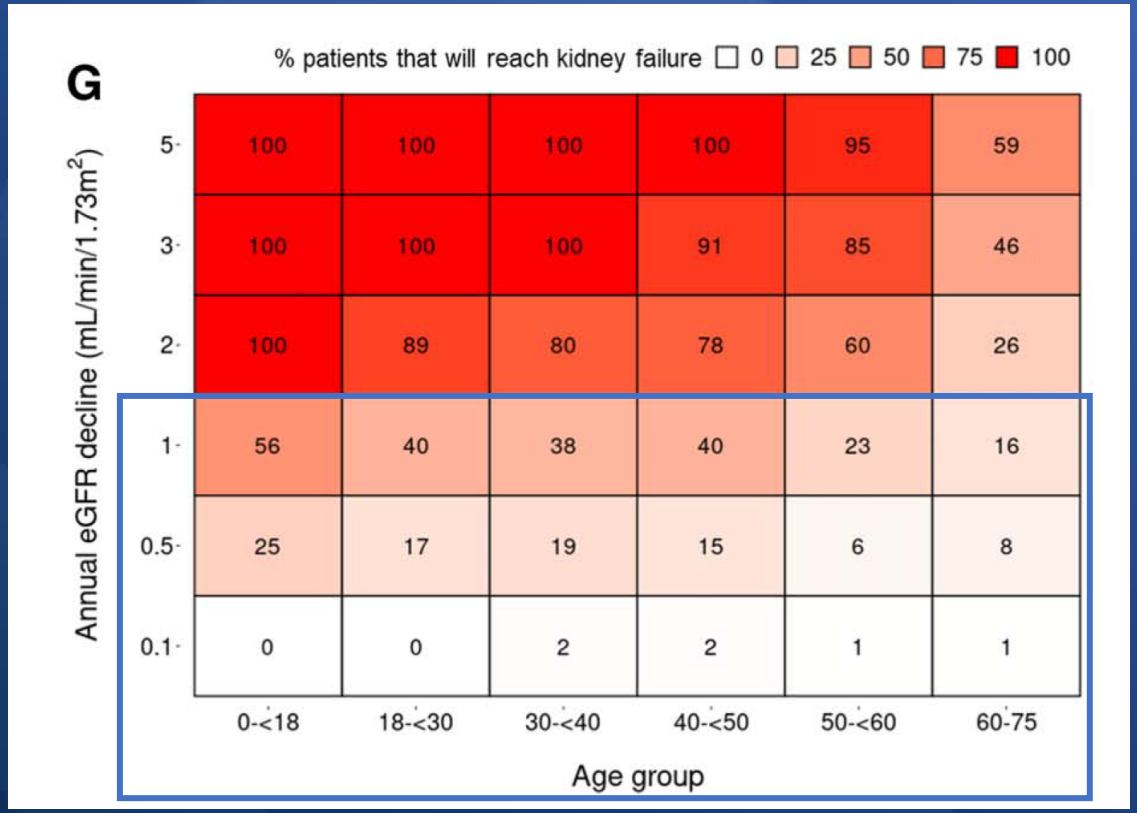


B cell depletion

B cell modulation

“Target the IgA-induced kidney damage-autoimmunity”

Optimised supportive kidney care

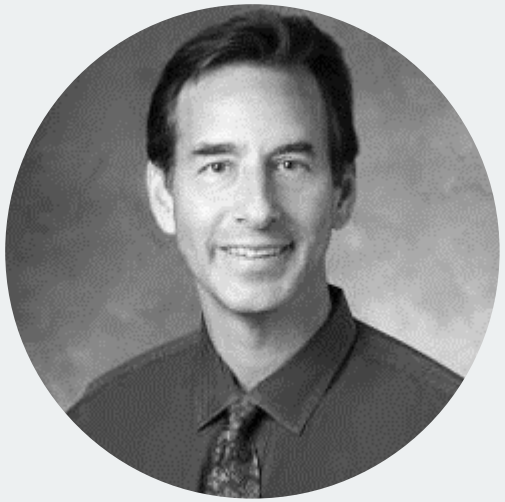


Pitcher D, et al. Clin J Am Soc Nephrol 2023

Agenda

Opening Remarks	**Marshall Fordyce, MD** Founder and CEO, Vera Therapeutics
IgAN Disease State	**Jonathan Barratt, PhD, FRCP** Professor, University of Leicester
Atacicept ORIGIN Phase 2b 72-week Results	**Richard Lafayette, MD, FACP** Professor, Stanford University
Closing Remarks	**Robert Brenner, MD** Chief Medical Officer, Vera Therapeutics
Q&A	

Richard Lafayette, MD, FACP



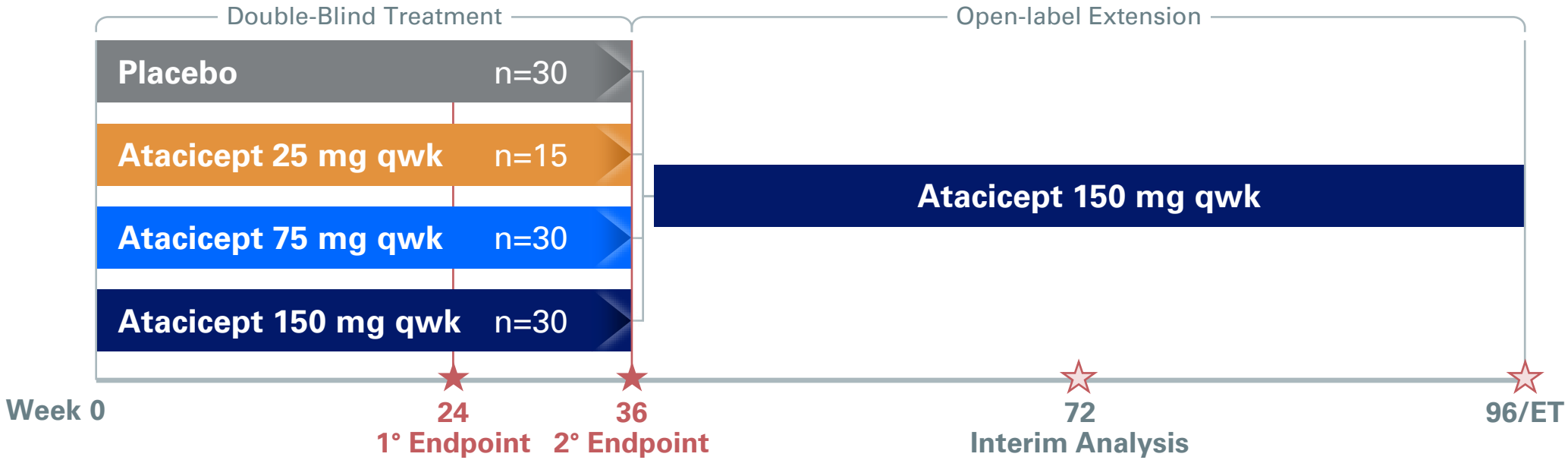
Stanford MEDICINE

Dr. Lafayette is a Professor of Medicine (Nephrology) and Director of the Stanford Glomerular Disease Center at Stanford University Medical Center. Dr. Lafayette completed his medical education at New York Medical College and went on to complete his residency at the Long Island Jewish Medical Center, and his fellowship at Stanford University School of Medicine. Dr. Lafayette is board-certified in Internal Medicine and Nephrology.

Dr. Lafayette served as the Associate Chair of the Stanford University Department of Medicine from 2002–2007, the Clinical Chief of Nephrology at Stanford University from 1999–2012, and currently serves as the Director of the Stanford Glomerular Disease Center since 2010. Dr. Lafayette was honored in America's Top Doctors, Best Doctors from 2004–2018, and received America's Top Doctors Award, Castle Connolly Medical Ltd. from 2014–2022. Dr. Lafayette has been part of the following boards and professional organizations: Editorial Board, Kidney News, American Society of Nephrology (2010–2021) Member, Glomerular Disease Advisory Committee, American Society of Nephrology (2013–2017) Member (ex-officio), Communications Committee, American Society of Nephrology (2015–Present).

ORIGIN Phase 2b IgAN Trial: Study Design and Objectives

Multinational, randomized, placebo-controlled trial



Inclusion Criteria

- Participants ≥18 years old with IgAN on renal biopsy and high risk of disease progression
- Stable and optimized RAASi for ≥12 weeks
- Use of SGLT2i allowed
- UPCR-24h >0.75 g/g or UP >0.75 g per 24h
- eGFR ≥30 mL/min/1.73 m^2
- Blood pressure ≤150/90 mmHg

Endpoints

- Primary efficacy: UPCR-24h at week 24 ★
- Key secondary: UPCR-24h at week 36 ★
- eGFR change up to week 96 ☆
- Gd-IgA1 change
- Safety

ET = end of treatment; Gd-IgA1 = galactose-deficient immunoglobulin A1; RAASi = renin-angiotensin-aldosterone system inhibitor; SGLT2i = sodium-glucose cotransporter-2 inhibitor; UPCR = urine protein:creatinine ratio.

Summary of Positive Phase 2b Week 36 Results

origin

- **Gd-IgA1 reduction of 64% from baseline with atacicept 150 mg**
- **Hematuria resolution in 80% of participants on atacicept 150 mg vs 5% on placebo**
- **Met primary endpoint, with statistically significant UPCR reductions on atacicept 150 mg**

PP Analysis	ITT Analysis	
Δ 43%*	Δ 35%*	*p<0.05

- **Stable eGFR observed for participants on atacicept, with clinically meaningful and statistically significant difference vs placebo**

Mean eGFR % change with atacicept 150 mg vs placebo was **11% (p=0.038)**, approximating to an absolute difference of **5.8 mL/min/1.73 m^2**

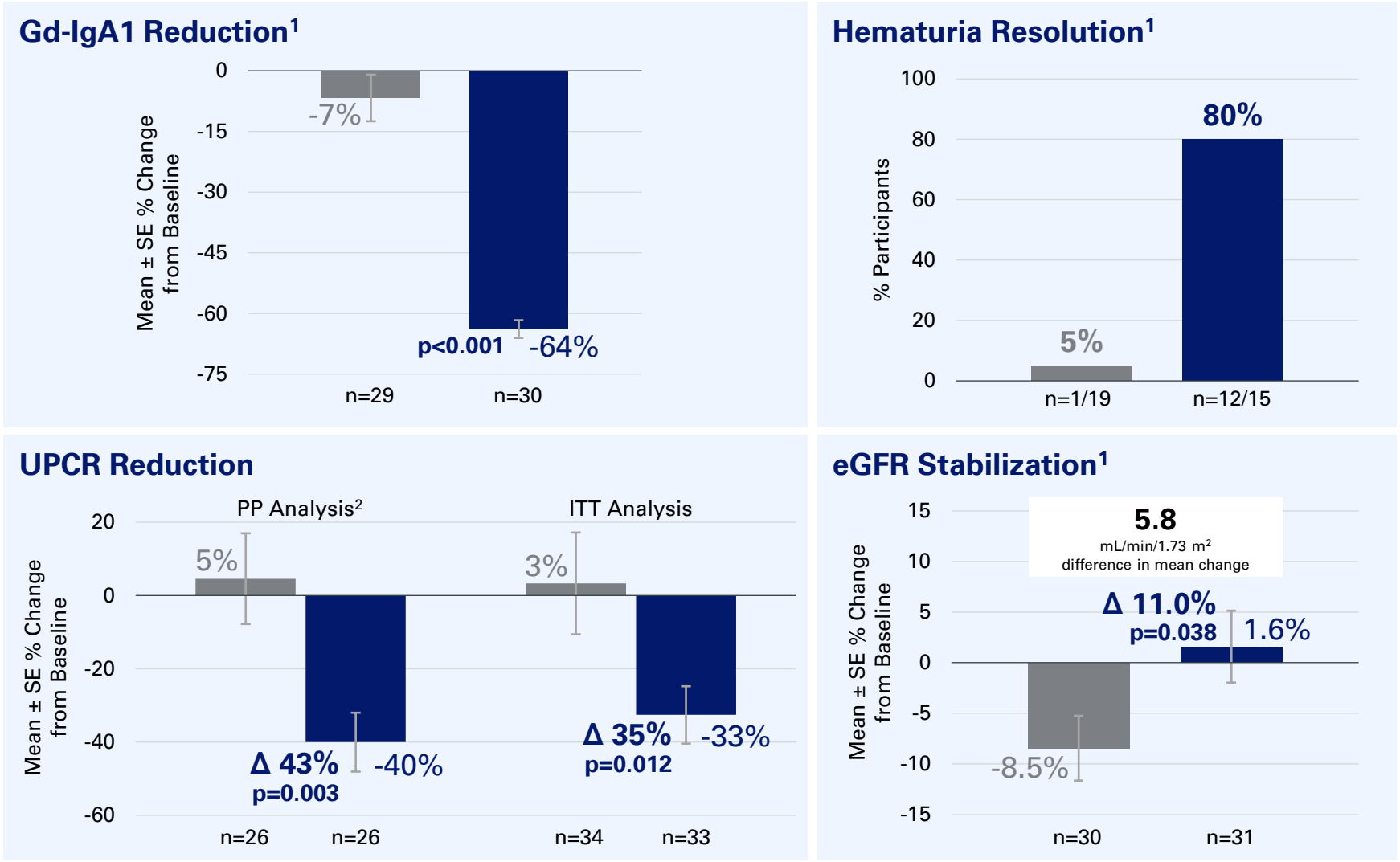
- **Clinical safety profile similar between atacicept and placebo**

Atacicept 150 mg dose selected for Phase 3 clinical trial, initiated in June 2023

ITT = intent to treat; PP = per-protocol. Hematuria resolution defined as decrease to negative/trace levels in participants with baseline hematuria 1+ or higher.
Lafayette R, et al. ERA 2023 late breaking clinical trial oral presentation, June 17 2023; Barratt J, et al. ASN 2023, SA-PO887.

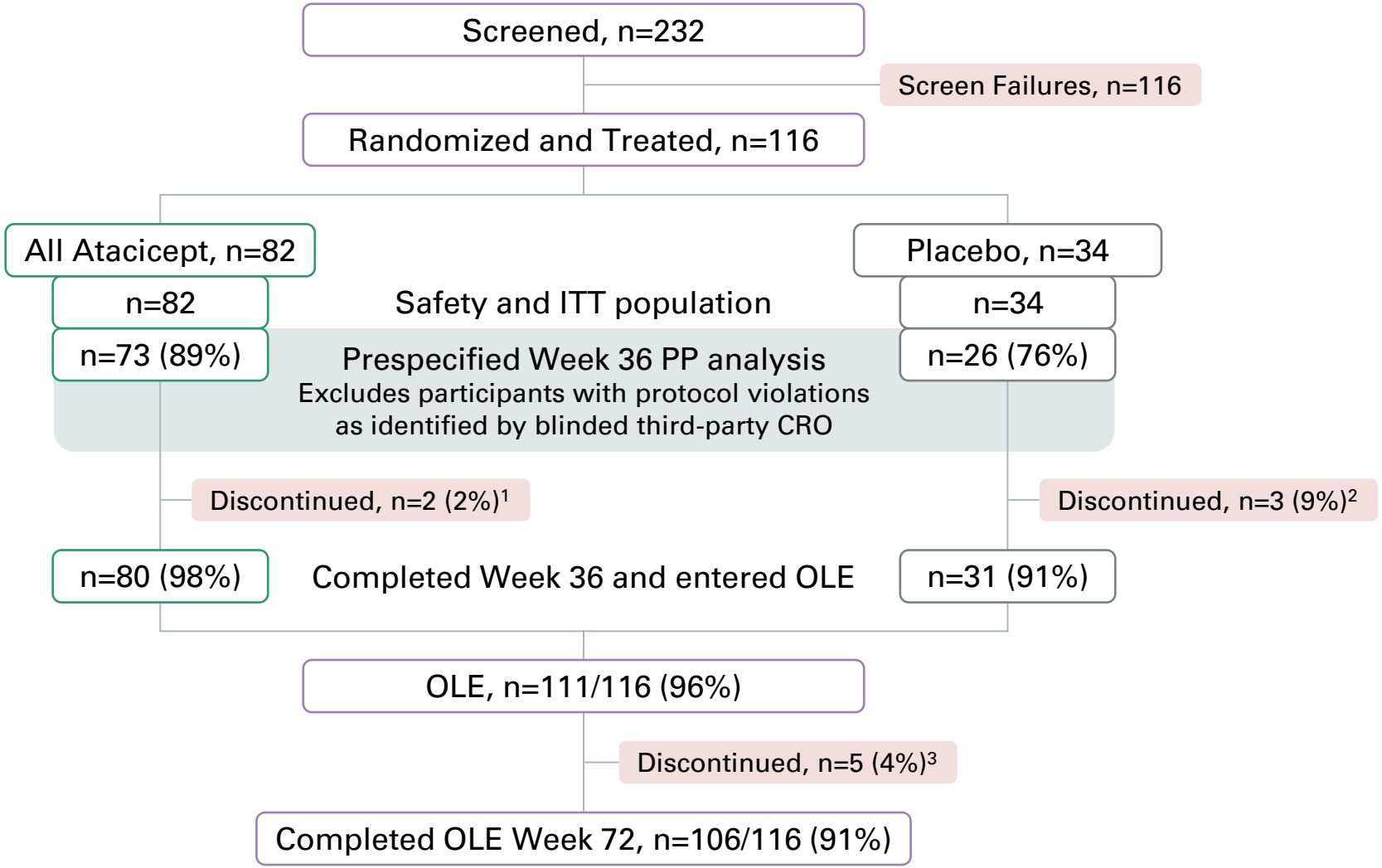
vera therapeutics

Disease Modification Observed in Phase 2b Week 36 Results



1. ITT analysis; 2. Prespecified Week 36 PP analysis excluded participants with protocol violations through week 36 as identified by blinded third-party CRO. Hematuria resolution defined as decrease to negative/trace levels in participants with baseline hematuria 1+ or higher. Lafayette R, et al. ERA 2023 late breaking clinical trial oral presentation, June 17 2023; Barratt J, et al. ASN 2023, SA-PO887.

ORIGIN 2b Participant Disposition



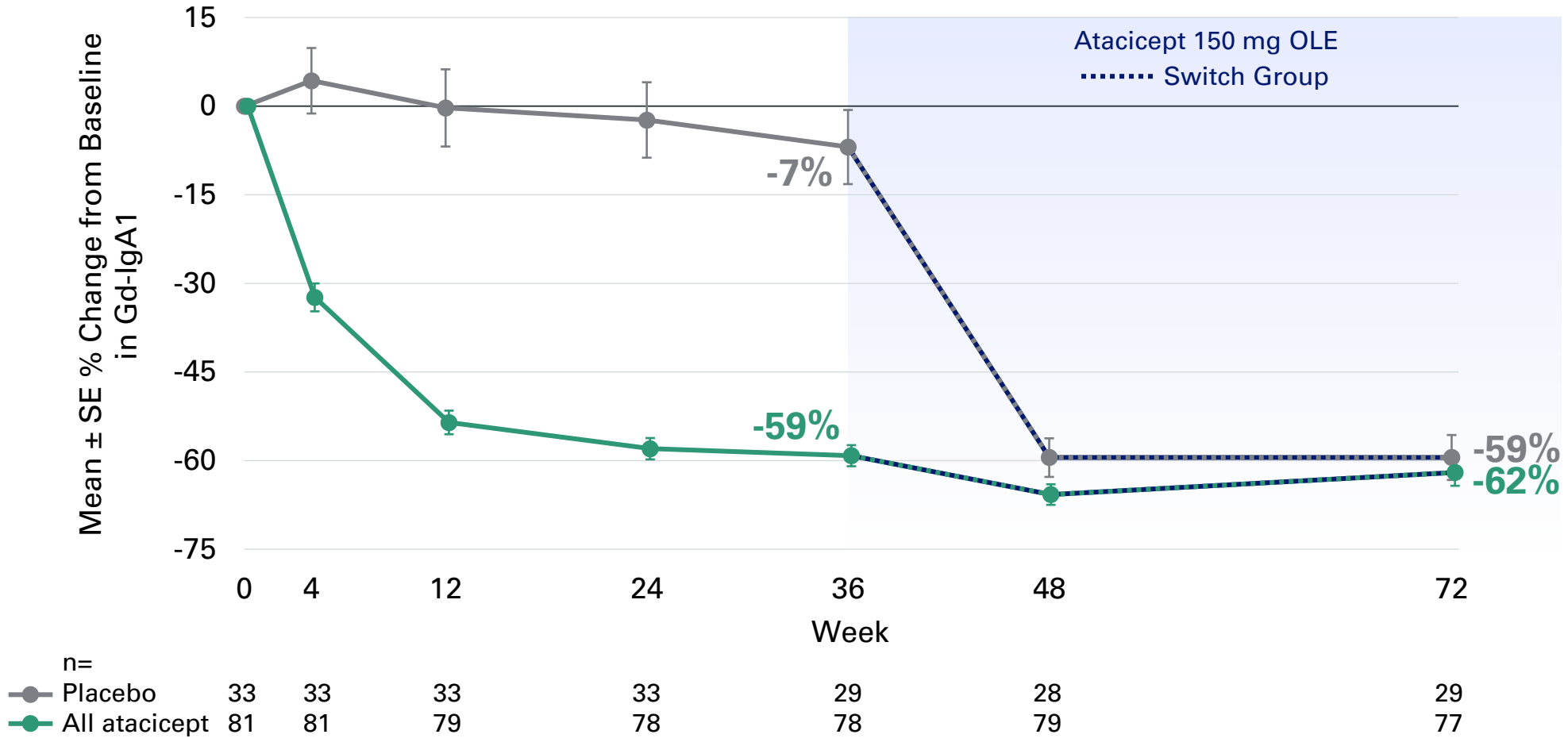
OLE = open label extension.
1. Discontinued to pursue elective surgery (1), discontinued due to positive hepatitis B DNA and adverse event (1).
2. Initiated prohibited medication for concomitant disease (1), discontinued due to plan to start prohibited medication for concomitant disease (1) and adverse event (1).
3. Discontinued to pursue surgery (1), discontinued due to serious adverse event of pneumonia in a heavy smoker, resolved (1), investigator decision (1), pregnancy (1), and participant withdrawal (1).

ORIGIN 2b Demographics and Baseline Characteristics

Mean ± SD or n (%)	Overall n=116	Atacicept 25 mg n=16	Atacicept 75 mg n=33	Atacicept 150 mg n=33	Placebo n=34
Age, y	39	40	41	38	39
Male sex	69 (59)	9 (56)	19 (58)	22 (67)	19 (56)
Race					
White	62 (53)	7 (44)	12 (36)	17 (52)	26 (76)
Asian	51 (44)	7 (44)	20 (61)	16 (48)	8 (24)
Other	3 (3)	2 (12)	1 (3)	0	0
eGFR, mL/min/1.73 m^2	63 ± 27.3	71 ± 28.7	64 ± 25.4	56 ± 22.7	66 ± 31.7
UPCR by 24h urine, g/g	1.6 ± 0.9	1.6 ± 0.8	1.7 ± 0.9	1.7 ± 1.0	1.6 ± 0.8
Time from biopsy, y	2.8 ± 2.8	1.7 ± 1.6	3.4 ± 2.8	3.3 ± 3.4	2.1 ± 2.4

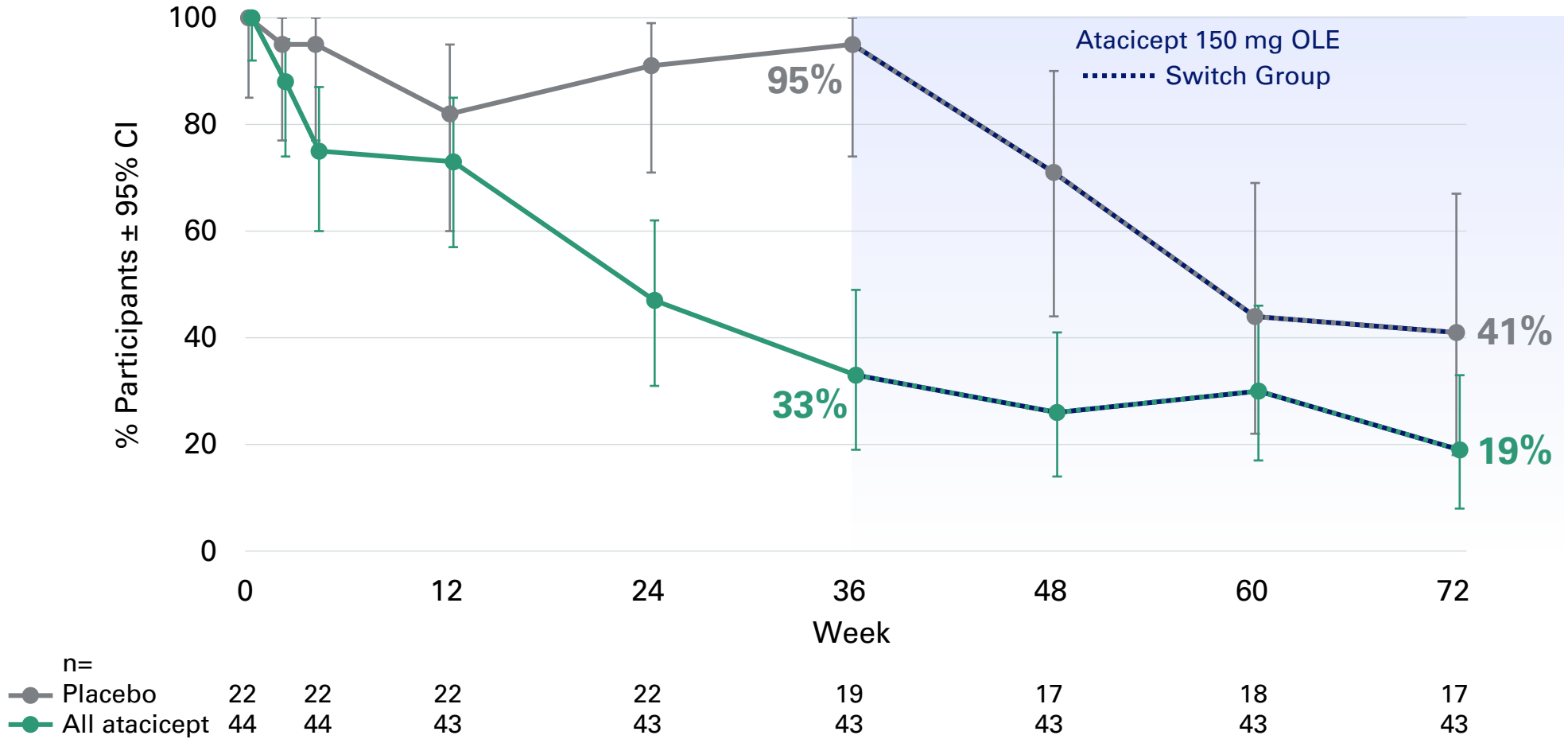
Consistent and Sustained Gd-IgA1 Reduction Through Week 72

Placebo → Atacicept Switch Group Had Similar Reduction as Randomized Atacicept Group



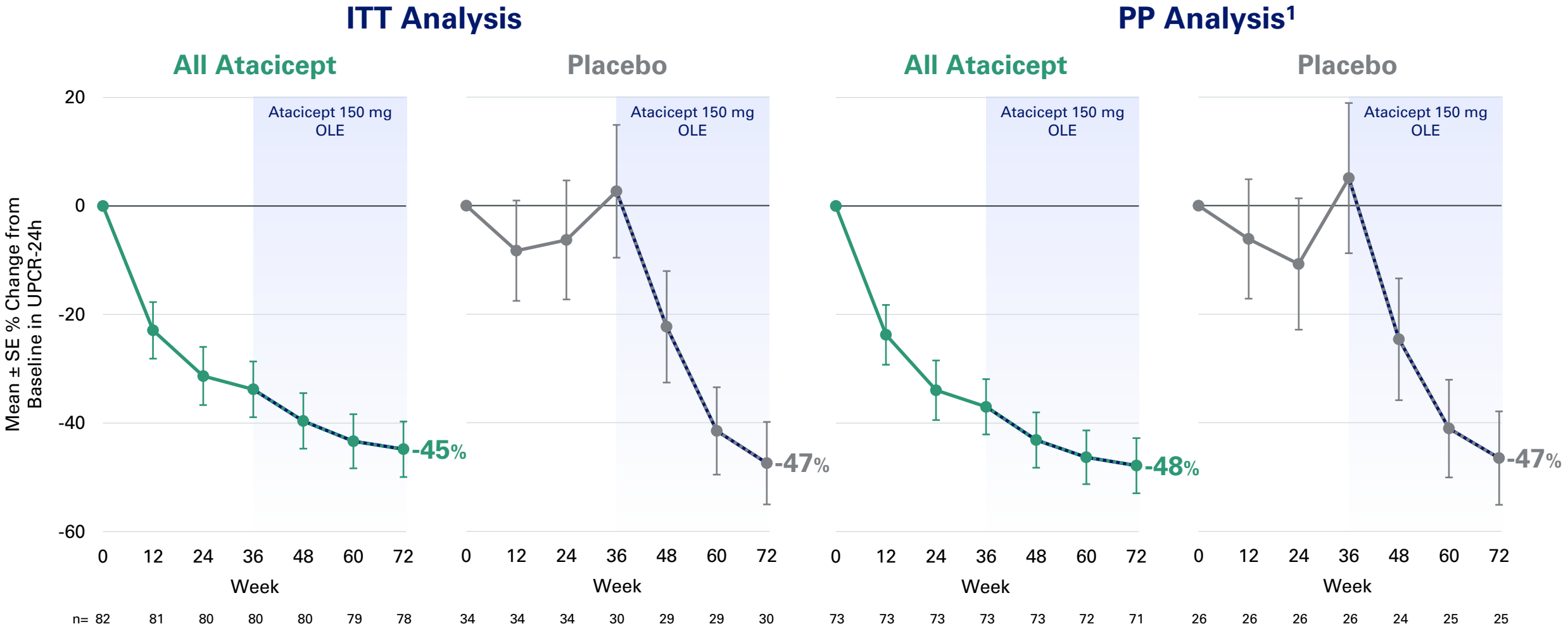
Percentage changes from baseline were computed using FDA-endorsed mixed-effects modeling; all atacicept group includes participants originally randomized to any atacicept group in the double-blind period; ITT analysis.

Consistent and Sustained Reductions in Percentage of Participants with Hematuria Through Week 72



Percentages represent number of participants with hematuria at each visit out of those with baseline hematuria; microscopic hematuria was evaluated via urine dipstick at a centralized lab, and hematuria levels were graded negative/trace, 1+, 2+, or 3+. All atacicept group includes participants originally randomized to any atacicept group in the double-blind period; ITT analysis. CI = confidence interval.

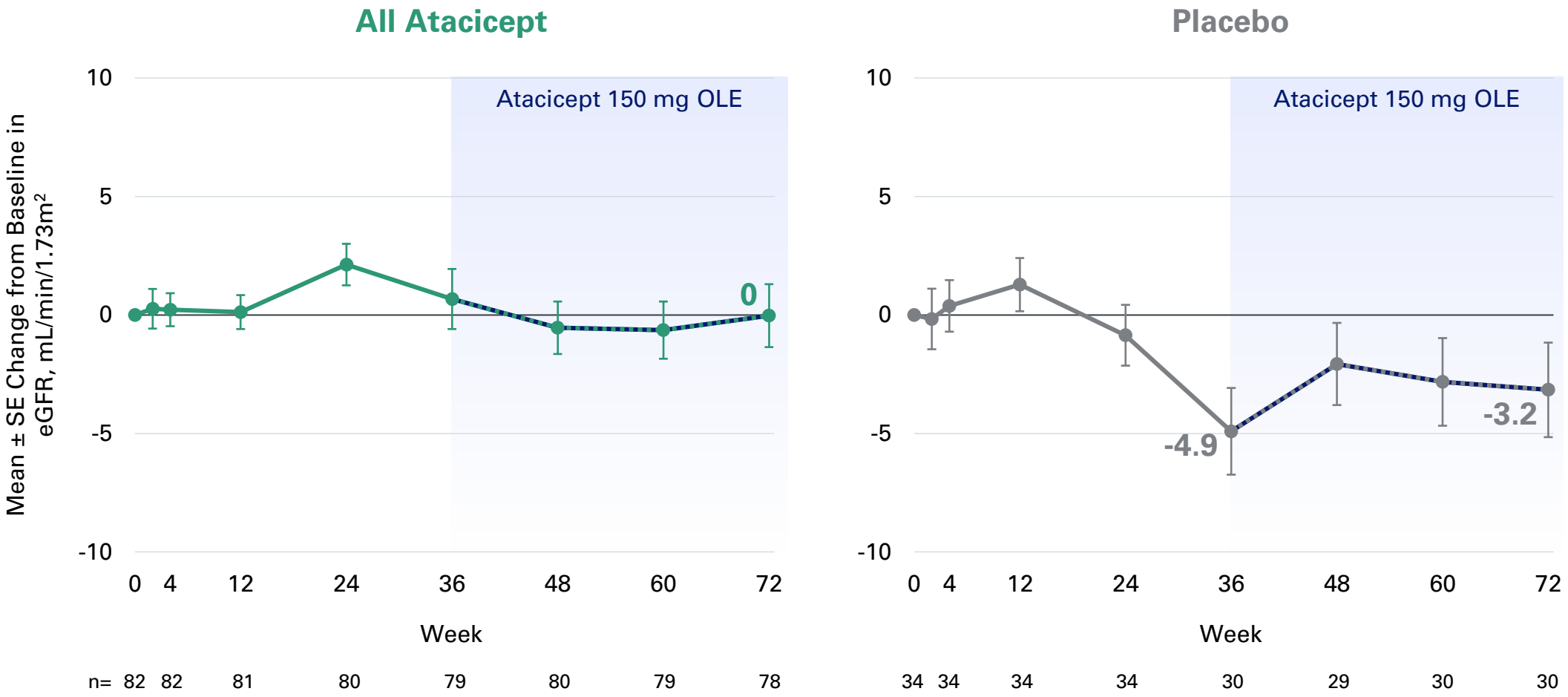
Consistent and Sustained Reductions in UPCR Over 72 Weeks



Percentage changes from baseline were computed using FDA-endorsed mixed-effects modeling which takes into account the effects of baseline UPCR and eGFR and implicitly imputes missing data as missing at random.
All atacicept group includes participants originally randomized to any atacicept group in the double-blind period.
1. Prespecified Week 36 PP analysis excluded participants with protocol violations through week 36 as identified by blinded third-party CRO.

Atacicept Resulted in eGFR Stabilization Through 72 Weeks

Atacicept Switch Halted eGFR Decline in Randomized Placebo Cohort



Percentage changes from baseline were computed using FDA-endorsed mixed-effects modeling which takes into account the effects of baseline UPCR and eGFR and implicitly imputes missing data as missing at random; geometric least squares (LS) means, ratio of geometric LS means, and standard errors (SE), were transformed back into the original scale from model estimates. All atacicept group includes participants originally randomized to any atacicept group in the double-blind period; ITT analysis.

OLE Adverse Events Profile Consistent with Randomized Period

Double-Blind Data Through Week 36; OLE Data Through 12/2023[1]

	Double-blind BL to W36				W36 to W72	BL to W72
Participants, n (%)	Placebo n=34	Atacicept 25 mg n=16	Atacicept 75 mg n=33	Atacicept 150 mg n=33	Total OLE Atacicept 150 mg n=111	Atacicept 150 mg n=33
TEAEs	28 (82)	11 (69)	24 (73)	25 (76)	77 (69)	26 (79)
Infections and infestations	11 (32)	6 (38)	16 (48)	13 (39)	33 (30)	15 (45)
Study drug-related TEAEs[2]	14 (41)	6 (38)	17 (52)	19 (58)	51 (46)	22 (67)
Serious TEAEs	3 (9)	0	1 (3)	1 (3)	8 (7)	2 (6)
TEAEs leading to study drug discontinuation	1 (3)[3]	0	0	1 (3)[4]	1 (1)[5]	1 (3)[4]
Deaths	0	0	0	0	0	0

- Total patient exposure:
  - OLE through 12/05/23: mean 48.8 wk, median 47.7 wk (range 10.7 – 62.7)
  - Double-blind BL to 12/05/23: mean 82.0 wk, median 83.4 wk (range 3.0 – 99.0)

1. W72 cut-off includes all safety data as of 12/05/23, including visits past W72. AEs are considered treatment-emergent during the OLE period if they start after the first dose of open-label atacicept 150 mg through the end of the study.
2. Majority of study drug-related TEAEs were injection site reactions and one contributed to drug discontinuation during double-blind period.
3. Discontinued due to worsening flank pain that was not resolved; unrelated to study treatment.
4. Discontinued due to injection site reaction and positive hepatitis B DNA that resolved without treatment 3 weeks later, normal liver function throughout.
5. Discontinuation due to pneumonia in a heavy smoker, resolved.

Summary of Week 72 Results

- Participants treated with atacicept for 72 weeks demonstrated:
  - Consistent and sustained reductions in Gd-IgA1, hematuria and UPCR
  - Consistent and stable eGFR
  - **In aggregate, these data provide evidence of long-term, comprehensive IgAN disease modification**
- Participants switched from placebo to atacicept demonstrated similar results (Gd-IgA1, hematuria, UPCR, eGFR) to those originally randomized to atacicept during the first 36 weeks of ORIGIN 2b
- The cumulative safety profile is consistent with that observed during the randomized 36 weeks of ORIGIN 2b
- Week 72 data provide additional confidence in the ongoing ORIGIN 3 study

Agenda

Opening Remarks	**Marshall Fordyce, MD** Founder and CEO, Vera Therapeutics
IgAN Disease State	**Jonathan Barratt, PhD, FRCP** Professor, University of Leicester
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Closing Remarks	**Robert Brenner, MD** Chief Medical Officer, Vera Therapeutics
Q&A	

IgAN Through the Ages

nephritis [*Greek*]: *nephros* "of the kidney" + *-itis* "inflammation"

~400 BC — Hippocratic Aphorism 7.34: earliest description of proteinuria[1]

"When bubbles settle on the surface of the urine, they indicate disease of the kidneys, and that the complaint will be protracted."

1791 — Signs/Symptoms of IgA vasculitis in patient in Vienna[2]

1763	Scarlet
1763	Erythema nodosum
Starting 1763	Chronic tooth maturation
1764	Angina tonsilaris
1765	Thyphus abdominalis
Starting 1766	Rheumatic fever
1767	Smallpox
1778	Influenza
Starting 1784	Recurrent renal colic
Starting 1784	Hypertension, epistaxis, cluster headache
Starting 1791	Depression, anancasm
5.12.1791	Death of uraemia

1968 — Evidence that IgAN is a B-cell mediated disease[3]

Les dépôts intercapillaires d'IgA - IgG

par MM. J. Berger et N. Hinglais (*)

with comments by
LILIANE STRIKER

Reprinted from J. Urol. Nephrol. (Paris) 74: 694–695, 1968

Sur les biopsies rénales de 25 malades, ont été mis évidence par immunofluorescence des dépôts intercapillaires fixant le sérum anti-IgA et moins intensément les sérums anti-IgG et anti-β_1 C-globuline. En revanche, il n'y avait aucune fixation sur ces dépôts, des sérums anti-IgM, anti-fibrinogène, anti-albumine, anti-coeruléoplasmine, anti-α_2-macroglobuline et anti-β-lipoprotéine. Les dépôts intercapillaires étaient présents dans tous les glomérules.

1998 — Discovery of APRIL[4]

APRIL, a New Ligand of the Tumor Necrosis Factor Family, Stimulates Tumor Cell Growth

By Michael Hahne,* Takao Kataoka,* Michael Schröter,* Kay Hofmann,§ Martin Irmler,* Jean-Luc Bodmer,* Pascal Schneider,* Tierry Bornand,* Nils Holler,* Lars E. French,‖ Bernard Sordat,§ Donata Rimoldi,‡ and Jürg Tschopp*

J. Exp. Med. © The Rockefeller University Press
Volume 188, Number 6, September 21, 1998 1185–1190

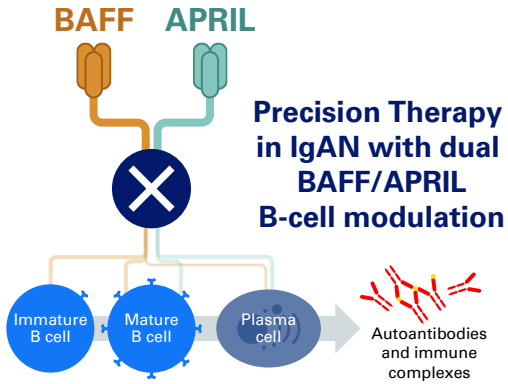
1999 — Discovery of BAFF[5]

BAFF, a Novel Ligand of the Tumor Necrosis Factor Family, Stimulates B Cell Growth

By Pascal Schneider,* Fabienne MacKay,¶ Véronique Steiner,* Kay Hofmann,‡ Jean-Luc Bodmer,* Nils Holler,* Christine Ambrose,¶ Pornsri Lawton,¶ Sarah Bixler,¶ Hans Acha-Orbea,* Danila Valmori,§ Pedro Romero,§ Christiane Werner-Favre,‖ Rudolph H. Zubler,‖ Jeffrey L. Browning,¶ and Jürg Tschopp*

J. Exp. Med. © The Rockefeller University Press
Volume 189, Number 11, June 7, 1999 1747–1756

Today — Precision Therapy in IgAN with dual BAFF/APRIL B-cell modulation



1. Diamandopoulos A, et al. Am J Kidney Dis 2009; 2. Hatzinger M, et al. Acta med-hist Adriat 2013; 3. Berger J, Hinglais N. J Am Soc Nephrol 2000; 4. Hahne M, et al. J Exp Med 1998; 5. Schneider P, et al. J Exp Med 1999.

Providing Context:

An Abbreviated Review of the CKD Therapy History and Landscape

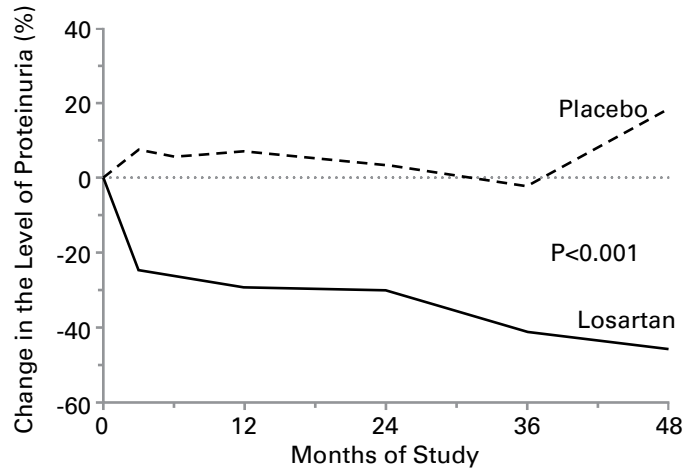
The NEW ENGLAND JOURNAL of MEDICINE

The Effect of Angiotensin-Converting-Enzyme Inhibition on Diabetic Nephropathy

Lewis EJ, et al. N Engl J Med 1993.

The NEW ENGLAND JOURNAL of MEDICINE

Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy

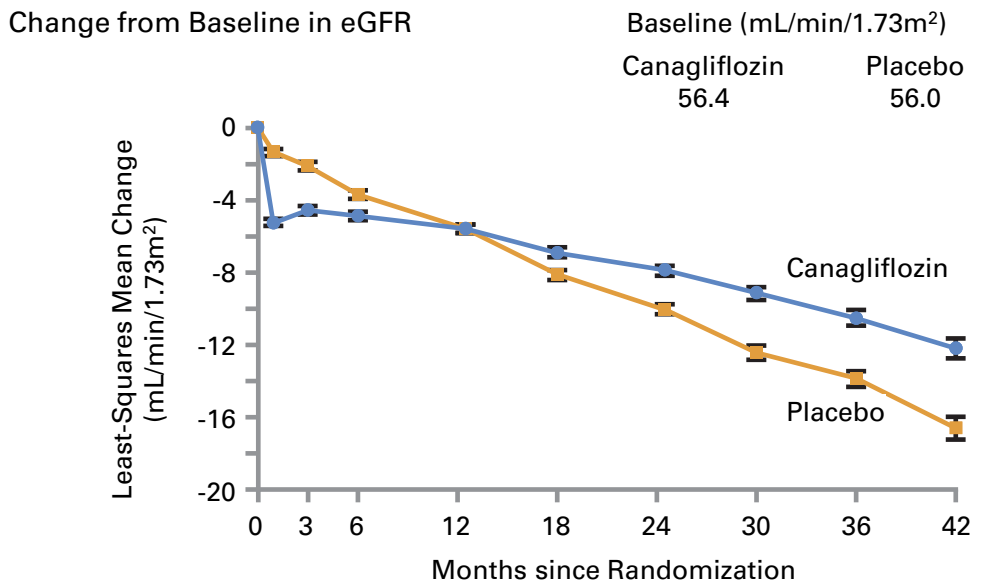


N at Risk					
Placebo	762	632	529	390	130
Losartan	751	661	558	438	167

Adapted from Brenner BM, et al. N Engl J Med 2001.

The NEW ENGLAND JOURNAL of MEDICINE

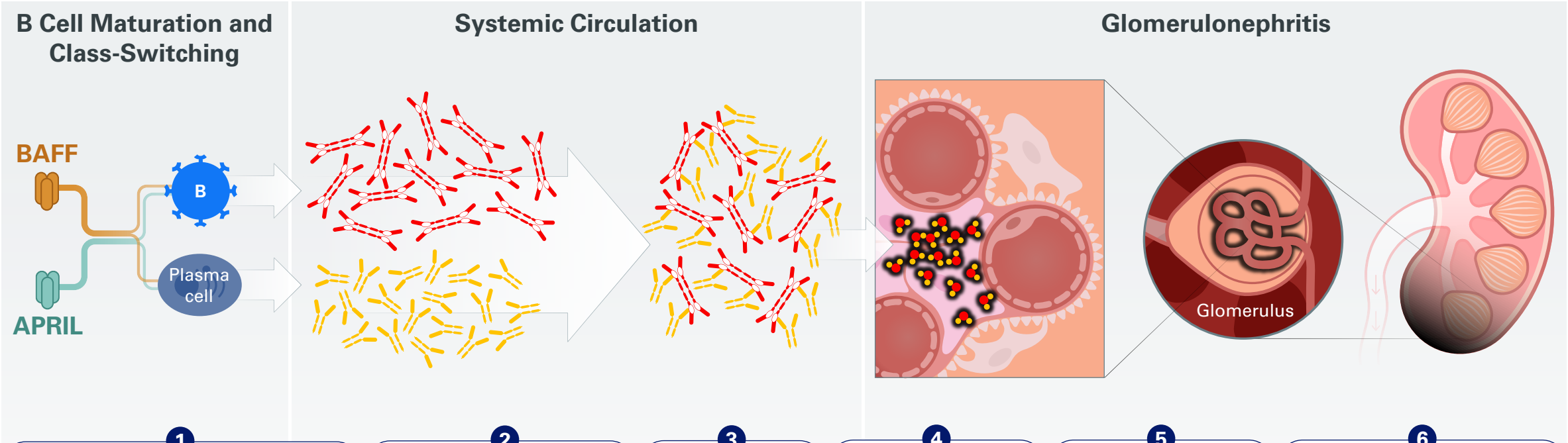
Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy



No. of patients								
Placebo	2178	1985	1882	1720	1536	1006	583	210
Canagliflozin	2179	2005	1919	1782	1648	1116	652	241

Adapted from Perkovic V, et al. N Engl J Med 2019.

IgAN is a Disease of B Cell Origin With Kidney Pathology

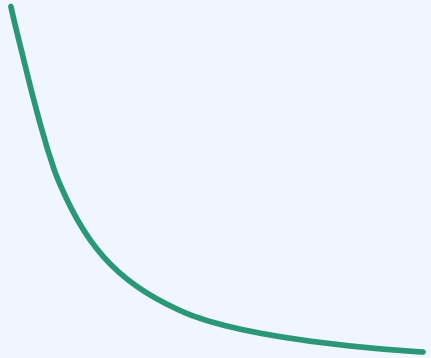


1. In response to various stimuli which upregulate BAFF and APRIL, Gd-IgA1 production by B cells is increased…
2. …autoantibodies bind to exposed Gd-IgA1 hinge region…
3. …and form immune complexes…
4. …which deposit in the mesangium…
5. …resulting in glomerular inflammation (nephritis)…
6. …and progressive kidney injury with hematuria, proteinuria, and eGFR decline

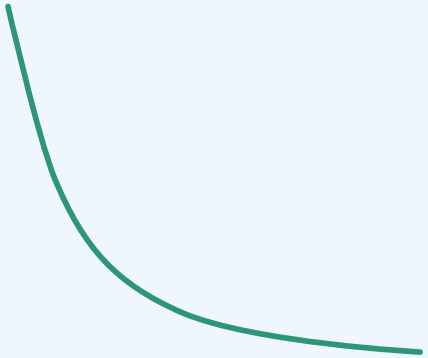
An Ideal IgAN Disease Modifying Therapy Would be Expected To…

1 → 2 → 3 → 4

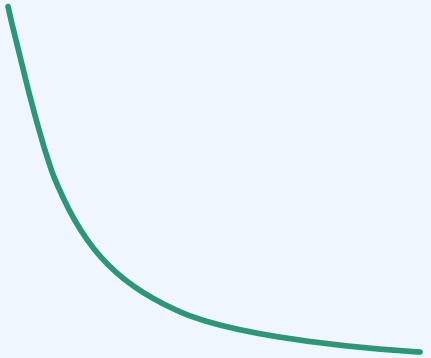
Reduce Gd-IgA1



Reduce hematuria



Reduce proteinuria

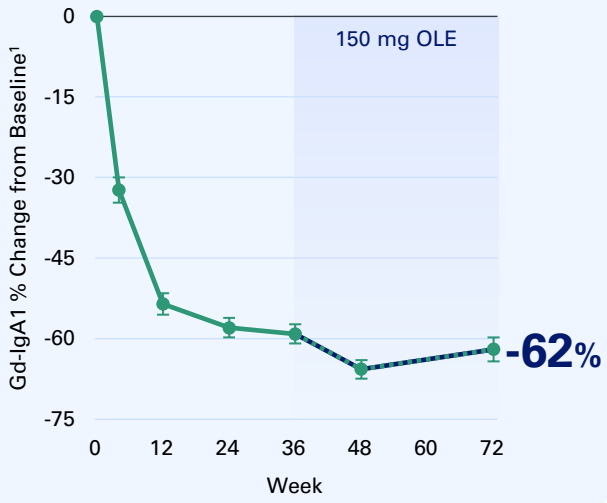


Stabilize eGFR

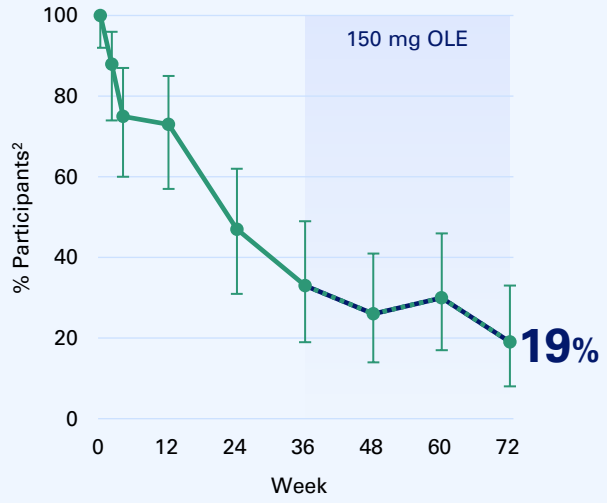
… And the Atacicept ORIGIN Phase 2b 72 Week Results Are Consistent With a Disease Modifying IgAN Profile

1 → 2 → 3 → 4

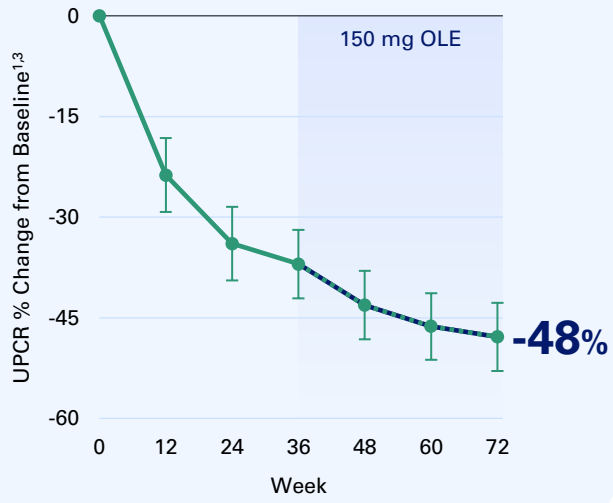
Reduction in Gd-IgA1



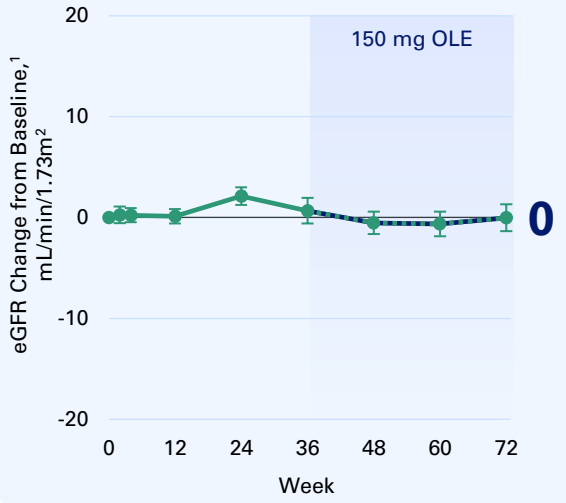
Reduction in patients with hematuria



Reduction in proteinuria

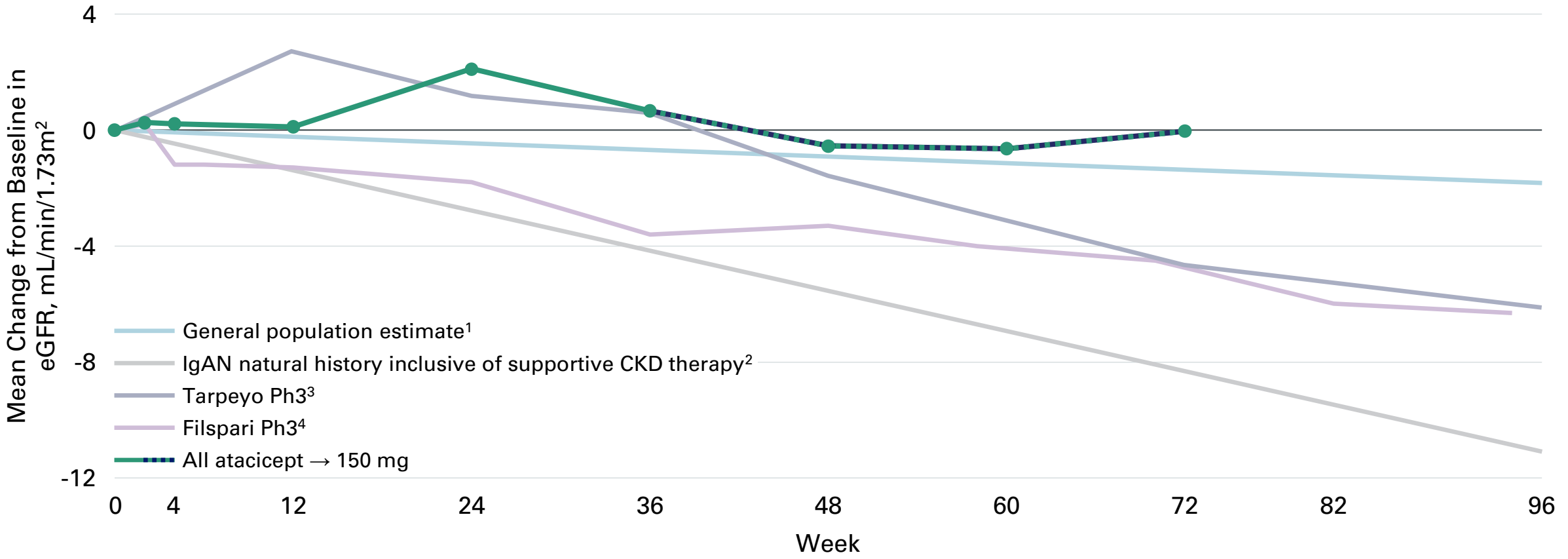


Stabilization of eGFR



1. Mean ± SE; 2. Percentages represent number of participants with hematuria at each visit out of those with baseline hematuria. Data from participants originally randomized to any atacicept group in the double-blind period in the ITT analysis for Gd-IgA1, hematuria, and eGFR, and in week 36 PP analysis for UPCR.

Atacicept Treated Participants Have an eGFR Profile Akin to the *General Population;* Dissimilar to Historical IgAN



This data is based on a cross-trial comparison and not a head-to-head clinical trial; such data may not be directly comparable due to differences in study protocols, conditions and patient populations.
Projected eGFR trajectories for general population and IgAN natural history do not represent clinical data and assume a constant eGFR slope over time. Figure cut at week 96 for consistency with Tarpeyo data.

1. Slope estimate from Baba M, et al. PLOS ONE 2015; 2. Average historical placebo slope from 7 clinical trials[3-11]; 3. Lafayette R, et al. Lancet 2023; 4. Travere Corporate Overview January 2024;
5. Li PK-T, et al. Am J Kidney Dis 2006; 6. Manno C, et al. Nephrol Dial Transplant 2009; 7. Lv J, et al. JAMA 2017; 8. Wheeler DC, et al. Kidney Int 2021; 9. Lv J, et al. JAMA 2022;
10. Zhang H, et al. ASN Kidney Week 2023, poster TH-PO1123; 11. Mathur M, et al. N Engl J Med 2023.

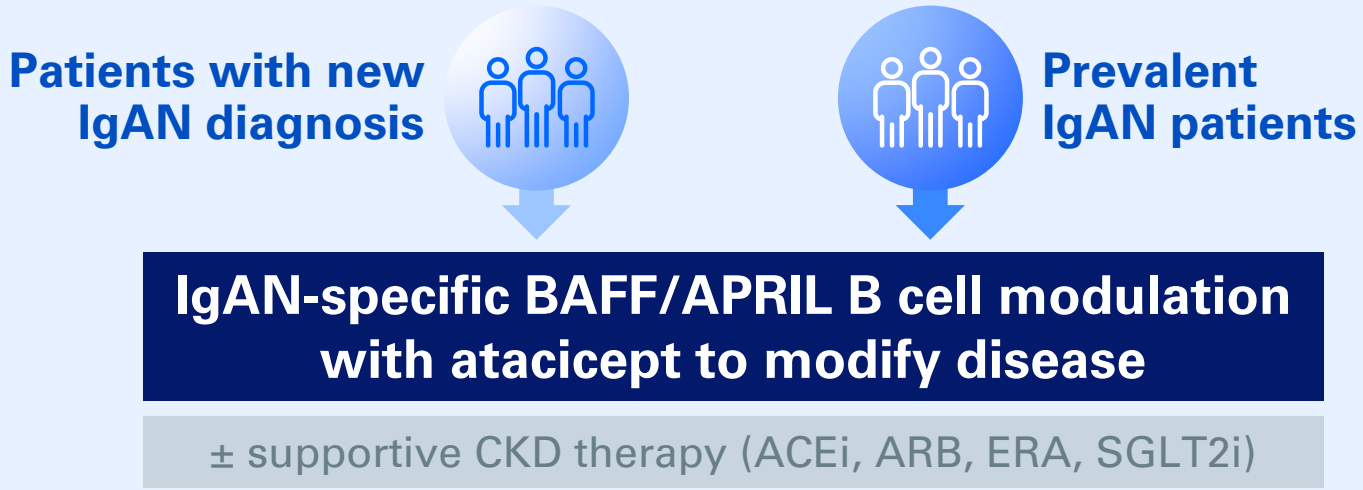
Cumulative Atacicept Data Offers Promise For Best-In-Class Potential…

…And Further Supports ORIGIN Phase 3 Design

	Atacicept	Sibeprenlimab[1]	Zigakibart[2]	Telitacicept[3]	Povetacicept[4]
Mechanism	BAFF/APRIL inhibition	APRIL inhibition only	APRIL inhibition only	BAFF/APRIL inhibition	BAFF/APRIL inhibition
Dosing & Administration	25/75/150 mg SC QW (Ph2) 150 mg SC QW (Ph3) 1 x 1 mL self-administered	2/4/8 mg/kg IV (Ph2) 400 mg SC QM (Ph3) 1 x 2 mL in-clinic injection	450mg IV Q2W (Ph2) 600mg SC Q2W (Ph3) 2 x 2 mL in-clinic injection	160/240 mg SC QW (Ph2) 3 x 1 mL injection	80/240 mg SC QM (Ph1b) 1 x TBD mL injection
Development Stage	Ph3	Ph3	Ph3	Ph2 discontinued in US no global development planned	Ph1b
Randomized Controlled Trial Data	✓	✓	✗	✓	✗
N (total pre-Phase 3)	132	155	40	44	20
Gd-IgA1 Reduction	62% at W72	~60% at W52	~70% at W40	50% at W24	~60% at W12
Hematuria	80% resolution at W36	Not reported	Not reported	Not reported	Not reported
UPCR Reduction vs Placebo	Δ 43% (p=0.003) at W36	Δ 43% at W36	No placebo controlled data	No UPCR data (different measure used)	No placebo controlled data
eGFR Duration Data	18 months 24 month pending	12 months	Not reported	6 months	6 months
Projected Commercial Launch	2026	2026	2027	Unknown	Unknown

This data is based on a cross-trial comparison and not a head-to-head clinical trial; such data may not be directly comparable due to differences in study protocols, conditions and patient populations.
Atacicept 150 mg data shown for W36, all-atacicept switch to 150 mg data shown for W72. 1. Mathur M, et al. NEJM 2023, Ph2 4 mg/kg IV Gd-IgA1 data, and Kooienga ASN 2022, TH-PO991, Ph2 pooled sibeprenlimab UPCR data; 2. Barratt J, et al. ERA-EDTA 2023, Ph2 combined cohort data; 3. Lv J, et al. Kidney Int Rep 2023 and Zan J, et al. Kidney Int Rep 2023, Ph2 240 mg data; 4. Tumlin J, et al. ASN 2023, TH-PO1125, Ph1b 80 mg data.

Potential Framework for a Future Treatment Paradigm in IgAN



- In prevalent IgAN patients, initiate disease modifying therapy with dual BAFF/APRIL B cell modulation using atacicept
- In incident IgAN patients with a fresh biopsy, initiate first line disease modifying therapy with dual BAFF/APRIL B cell modulation using atacicept
- Add/continue nonspecific supportive CKD therapy (ACEi, ARB, ERA and SGLT2i) for additional benefit
- With disease modifying therapy, the rationale for steroids and complement inhibitors may not exist

ERA = endothelin receptor antagonist.

Congruency with ORIGIN 2b Instills Greater Confidence in ORIGIN 3; Enrollment On Track

origin3

Initiated in 2023

Inclusion Criteria

- Patients ≥18 years old with IgAN on kidney biopsy 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 m^2
- Blood pressure ≤150/90 mmHg

Endpoints

- Primary efficacy: UPCR-24h at week 36 ★ to support potential accelerated approval
  - >90% power at week 36
- Key secondary: eGFR change up to week 104 ☆
  - 90% power for eGFR Δ 4 mL/min at week 104
- Safety

- Operational efficiency leveraging similar study design and worldwide sites as ORIGIN 2b
- Same self-administered SC formulation and dose as used in ORIGIN 2b

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2024 Poised To Be An Impactful Year Of Community Engagement

Q1

5th CKD Summit
Chronic Kidney Disease Drug Development

- Community engagement

Q2

NATIONAL KIDNEY FOUNDATION
SCOM24
SPRING CLINICAL MEETINGS

- Community engagement

ISN WCN'24
Hosted by SAN SLANH

- Encore data accepted as posters
- Industry sponsored symposium
- Community engagement

Q3

61ST ERA CONGRESS
STOCKHOLM & VIRTUAL
MAY 23-26, 2024

- Data submission
- Industry sponsored symposium
- Community engagement
- Medical Affairs booth presence

Q4

AMERICAN SOCIETY OF NEPHROLOGY · ASN ·
KIDNEY WEEK

- Data submission
- Community engagement
- Sponsorship of GN CME course
- Medical Affairs booth presence

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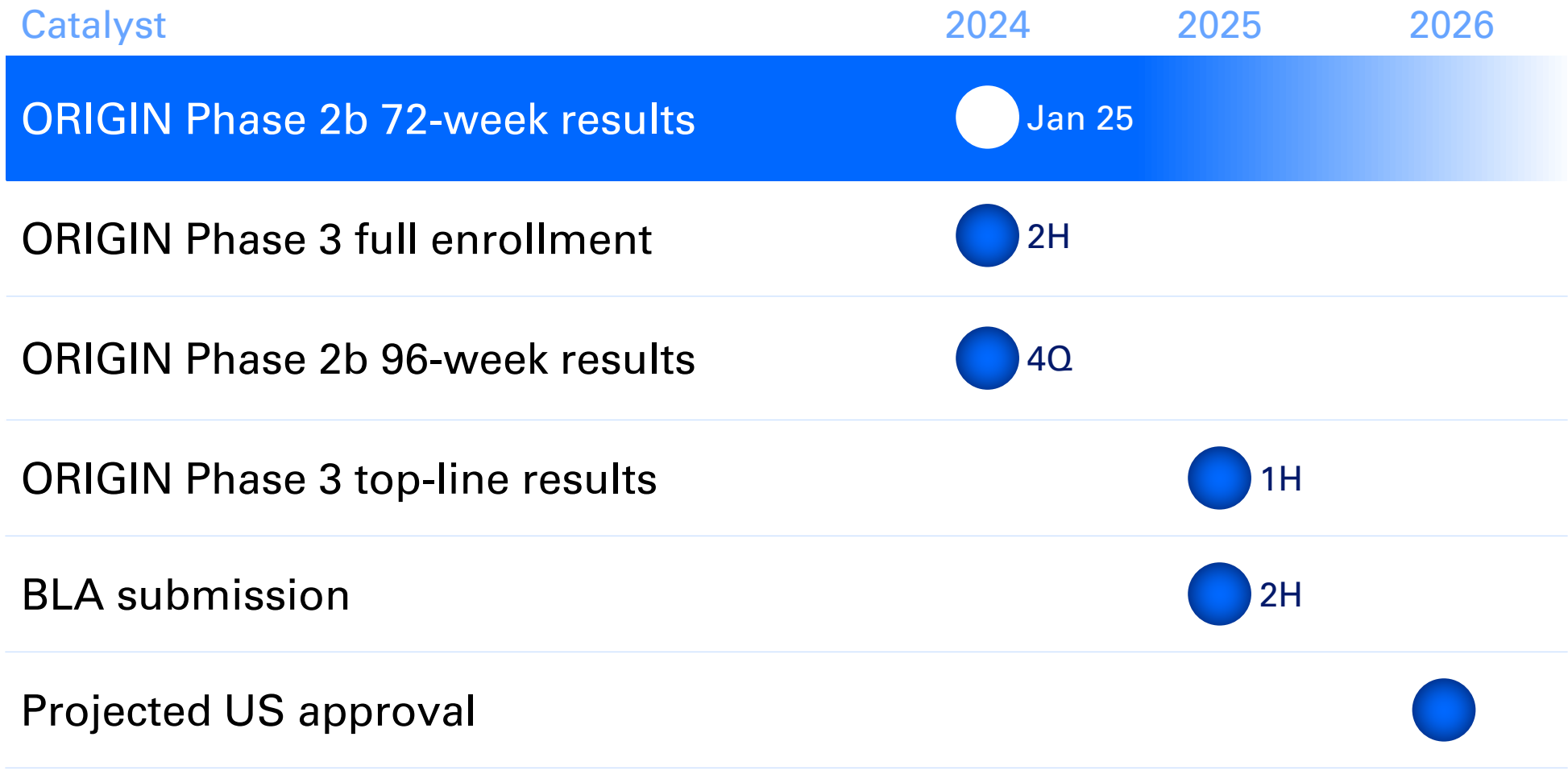
Atacicept: Anticipated Clinical & Regulatory Catalysts Over Next 18 Months



Based on management's current assumptions.

Returning to Vienna in the late 18th Century…

- We have record of a 35-year-old man living in Vienna, with a history of various infections, depression and headache
- Not long before his death, he was noted to have skin rash, gastroenteritis and edema
- He died on December 5, 1791

1763	Scarlet
1763	Erythema nodosum
Starting 1763	Chronic tooth maturation
1764	Angina tonsilaris
1765	Thyphus abdominalis
Starting 1766	Rheumatic fever
1767	Smallpox
1778	Influenza
Starting 1784	Recurrent renal colic
Starting 1784	Hypertension, epistaxis, cluster headache
Starting 1791	Depression, anancasm
5.12.1791	Death of uraemia

Hatzinger M, et al. Acta med-hist Adriat 2013.

In summary, a 35-year-old man died after a fortnight's acute illness characterized by painful and swollen hands and feet at its onset. He was feverish and later developed more generalized swelling, severe weakness, vomiting and diarrhoea. He may have had a rash. He was not dyspnoeic - he could sing - and his consciousness was unclouded until very shortly before death.

For some 2 or 3 months before this illness he had been pale and subject to lapses of consciousness, and had complained of loin pain. For one to two years he had suffered intermittent headaches and depression. He had a history of possible renal colic and, in childhood, typhoid and smallpox. He may have had atypical rheumatic fever and perhaps hepatitis.

Wheater M. J Royal Society Med 1990.

Wolfgang Amadeus Mozart

Perhaps the First Described Individual to Succumb to an IgA Mediated Death

- Mozart displayed signs and symptoms of IgA Vasculitis, and it is believed he ultimately died due to kidney failure
- He remained engaged and composing, working on the Lacrymosa of the *Requiem,* within hours of his ultimate demise
- Imagine if Mozart lived in an era during which B cell modulation of human disease was possible, potentially resulting in 50 more years of his genius composition for the world to enjoy
- More importantly, we recognize that for all current and future Mozarts, the possibility of bringing forward a true disease modifying therapy for IgAN and other B cell mediated diseases is our great collective opportunity

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