



## Oral Communications 5 Glomerular Diseases (GN)

**December 6, 2025 (Saturday) 09:30~11:00**

**Venue : Room 8 (602)**

Chair(s)

Desmond Yap, Shih-Yuan Hung

09:30-09:39

Dissecting the Role of ATF6 $\alpha$  and ATF6 $\beta$  in Podocyte Homeostasis and Injury Response  
APCN20250939

**Maidina Saifuding**  
Division of Chronic Kidney Disease Pathophysiology, Graduate School of Medicine, The University of Tokyo

09:39-09:48

Single-Cell Profiling Reveals WTAP Deficiency in Podocytes as a Key Mediator of Podocyte Injury and FSGS Pathogenesis  
APCN20250345

**Yanfeng Lu**  
Department of Nephrology, The First Affiliated Hospital of Zhengzhou University

09:48-09:57

FABP5 Involved in C5a Triggering ROS and Mitochondrial Damage in Podocytes  
APCN20250572

**I-Jung Tsai**  
Division of Nephrology, Department of Pediatrics, National Taiwan University Hospital

09:57-10:06

Single-Cell Transcriptomics Reveals Age-Dependent Transdifferentiation Potential of Glomerular Parietal Epithelial Cells  
APCN20250205

**Heng Wang**  
Centre for Transplant and Renal Research, Westmead Institute for Medical Research, The University of Sydney

10:06-10:15

Evaluation of Hematuria in Patients Treated With Ravulizumab in The Phase 2 SANCTUARY Trial  
APCN20250497

**Jonathan Barratt**  
Department of Cardiovascular Sciences, University of Leicester

10:15-10:24

Use of Immunosuppression in Severe Paediatric IgA Nephropathy: A Multi-National Multi-Centre Study  
APCN20250810

**Fanny Ho**  
Paediatric IgAN Study Group





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10:24-10:33	Longer Follow-Up of Povetacicept Shows Potential for Treatment of IgA Nephropathy (RUBY-3 Study) APCN20250777	<b>Sreedhar Mandayam</b> University of Texas MD Anderson Cancer Center
10:33-10:42	Impact of Endocapillary Proliferation and Membranous Histology on Patient Outcomes Among Southeast Asians With Lupus Nephritis APCN20250597	<b>Julia G Andres</b> Department of Renal Medicine, Singapore General Hospital, SingHealth-Duke NUS Academic Medical Center
10:42-10:51	Efficacy of Ravulizumab on Proteinuria Response by Baseline Proteinuria or eGFR: A Post Hoc Analysis of the SANCTUARY Trial APCN20250489	<b>I-Ru Chen</b> Division of Renal Transplantation, Division of Nephrology and the Kidney Institute, Department of Internal Medicine, China Medical University Hospital
10:51-11:00	Change in Soluble Biomarker Levels in Patients With IgA Nephropathy: An Analysis of The Phase 2 Trial of Ravulizumab (SANCTUARY) APCN20251025	<b>Jonathan Barratt</b> Department of Cardiovascular Sciences, University of Leicester

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## Oral Communications : Glomerular Diseases (GN)

Abstract Submission No. : APCN20250939

### Dissecting the Role of ATF6 $\alpha$ and ATF6 $\beta$ in Podocyte Homeostasis and Injury Response

MAIDINA SAIFUDING<sup>1,2</sup>; Midori Sakashita<sup>1,2</sup>; Masaomi Nangaku<sup>2</sup>; Reiko Inagi<sup>1</sup>

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#### Abstract

##### Introduction

Activating transcription factor 6 (ATF6), a key sensor of the unfolded protein response (UPR), is crucial for maintaining endoplasmic reticulum (ER) homeostasis and is implicated in various kidney diseases characterized by maladaptive UPR, known as ER stress. While ATF6's role in renal physiology is recognized, its specific function in podocytes remains unclear. ATF6 has two isoforms, ATF6 $\alpha$  and ATF6 $\beta$ , we generated podocyte-specific ATF6 $\alpha\beta$  conditional knockout mice (ATF6 $\alpha\beta$  cKO) to explore its role in podocyte homeostasis and glomerular injury.

##### Methods

To model glomerular injury, ATF6 $\alpha\beta$  cKO mice and wild-type (WT) littermates were treated with nephrotoxic serum to induce anti-GBM nephritis. Renal function was assessed from Day 0 to Day 21 by measuring urinary albumin-to-creatinine ratio (ACR). PAS staining and immunohistochemistry (IHC) were used to evaluate podocyte loss, and tubular damage. Gene expression analyses of UPR and ER-associated degradation (ERAD) pathways were performed via RT-qPCR and immunoblotting, focusing on ATF6 downstream targets including Derl3 and SDF2L1.

##### Results

Under basal conditions, ATF6  $\alpha\beta$  cKO mice exhibited no significant differences in renal function or glomerular architecture compared to WT controls. Following induction of anti-GBM nephritis, ACR peaked on day 4 after disease induction and gradually declined thereafter but did not return to baseline during the experimental period. The increased ACR were associated with podocyte damage (podocyte loss and decreased nephrin expression) and subsequent tubular damage. However, podocyte-specific ATF6 $\alpha\beta$  deficiency developed comparable levels of kidney dysfunction and podocyte damage, with no statistically significant differences observed. Notably, in WT mice, the expression of UPR sensors, PERK, IRE1, and ATF6, declined progressively during anti-GBM nephritis, reaching a nadir at Day 4. This was accompanied by a marked reduction in ERAD-related genes such as Derl3 and SDF2L1, which are responsible for clearing misfolded proteins. In contrast, in ATF6 $\alpha\beta$  cKO mice, podocyte-specific ATF6 deficiency led to a further decline in Derl3 and SDF2L1 expressions, indicating the contribution of podocyte ATF6 to the ERAD system, although it is dispensable for anti-GBM nephritis progression.

##### Conclusion

Our findings suggest that ATF6 signaling is not essential for maintaining baseline glomerular function or responding to acute podocyte injury at renal functional and histological levels. However, ATF6 may support ER quality control through ERAD during anti-GBM nephritis progression. Although dispensable under glomerular stress, podocyte ATF6 may enhance the ER stress responses, indicating an auxiliary yet functionally important role in maintaining proteostasis under pathological conditions. These results provide new insights into the ATF6-dependent adaptive mechanisms in podocyte injury.

**Keywords** : ATF6, podocyte, anti-GBM disease

## Oral Communications : Glomerular Diseases (GN)

Abstract Submission No. : APCN20250345

### Single-Cell Profiling Reveals WTAP Deficiency in Podocytes as a Key Mediator of Podocyte Injury and FSGS Pathogenesis

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<sup>1</sup> Department of Nephrology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China.

#### Abstract

**Introduction:** Focal segmental glomerulosclerosis (FSGS) is a leading cause of end-stage renal disease (ESRD), with podocyte injury as core pathological feature. Despite ongoing research efforts, current treatment options remain limited. Genetic factors and the complexity of gene regulatory networks that have yet to be fully resolved. Therefore, this study aims to discover and elucidate the novel pathogenic gene *Wtap* and its underlying mechanisms in FSGS.

**Methods:** Immunofluorescence was employed to detect WTAP expression in podocytes of human FSGS patients and adriamycin (ADR)-induced FSGS mouse models. Two distinct podocyte-specific *Wtap* knockout mouse models were generated using the Cre-loxP system: a rapidly developing constitutive knockout (cKO) model and a tamoxifen-induced conditional knockout (iKO) model. Renal function alterations were assessed via ELISA, while renal pathological changes were examined using HE and PAS staining. Single-cell RNA sequencing (scRNA-seq) was performed to analyze changes in renal cell types in cKO mice. CellChat was utilized to investigate intercellular communication among various renal cell types in the cKO model. Serum and urine SPP1 levels were measured by ELISA, and cKO mice were treated with intraperitoneal injections of SPP1-neutralizing antibodies for two weeks to evaluate therapeutic effects on renal pathology.

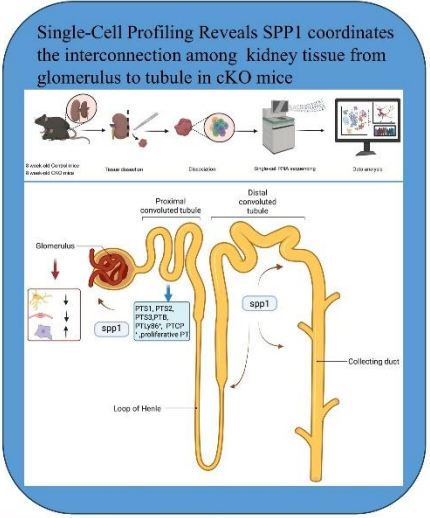
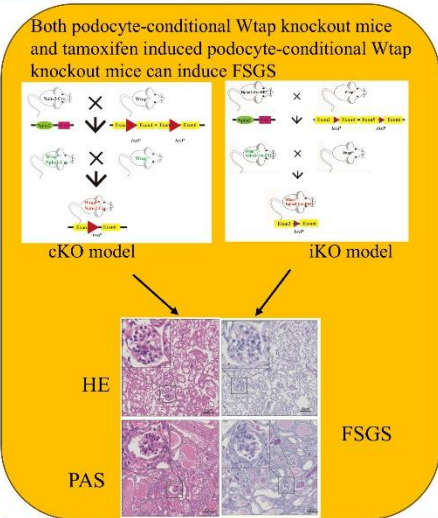
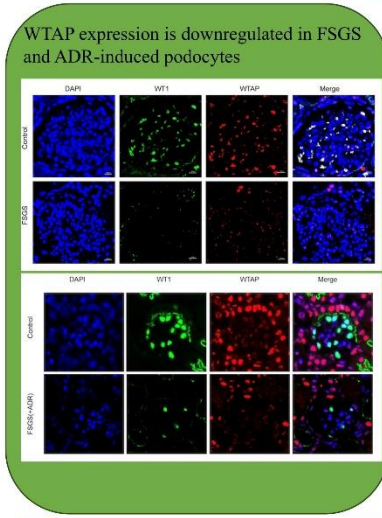
**Results:** Our findings revealed a significant reduction in WTAP expression in podocytes of both FSGS patients and ADR-induced mouse models. We successfully established two podocyte-specific *Wtap* knockout mouse models. Both models exhibited progressive FSGS glomerular pathological changes. scRNA-seq results demonstrated a marked decrease in the proportions of podocytes, endothelial cells, and tubular cells in cKO mice, alongside a significant increase in mesangial cells and inflammatory cells, including T cells, macrophages, and fibroblasts. Differential gene expression analysis in podocytes indicated the activation of PANoptotic signaling in cKO mice. Furthermore, in vitro experiments using WTAP-knockout human podocytes (HPCs) confirmed the occurrence of PANoptosis in podocytes. Additionally, we analyzed intricate cell-cell interactions from glomeruli to tubules in the kidneys of control and cKO mice. Cell communication analysis revealed that SPP1 mediates intercellular signaling between glomeruli and tubules in cKO mice. ELISA detected significantly elevated SPP1 levels in serum and urine. Notably, treatment with SPP1-neutralizing antibodies substantially ameliorated renal injury in cKO mice.

**Conclusion:** WTAP expression is significantly downregulated in podocytes of FSGS kidneys, and podocyte-specific knockout of WTAP leads to podocyte injury and FSGS development. Moreover, inhibition of the SPP1 signaling pathway improves renal pathological changes in cKO mice.

**Keywords :** Key Words: FSGS, WTAP, PANoptosis, ScRNA-seq, spp1

# Single-Cell Profiling Reveals WTAP Deficiency in Podocytes as a Key Mediator of Podocyte Injury and FSGS Pathogenesis

APCN x TSN 2025



Lu et al, 2025

Conclusion: WTAP deficiency in podocytes can induce podocyte injury and FSGS by activating SPP1 signal pathway.

## Oral Communications : Glomerular Diseases (GN)

Abstract Submission No. : APCN20250572

### **FABP5 involved in C5a triggering ROS and mitochondrial damage in podocytes**

I-JUNG TSAI<sup>1</sup>; Wei-Chou Lin<sup>2</sup>; Yu-Lin Tseng<sup>1</sup>; Yen-Hung Lin<sup>3</sup>; Chia-Hung Chou<sup>4</sup>; Yong-Kwei Tsau<sup>1</sup>

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#### **Abstract**

##### **Background**

We investigated human kidney biomarker expression in plasma and urine from patients with steroid-sensitive nephrotic syndrome (SSNS) and severe steroid-dependent nephrotic syndrome (SDNS) during both relapse and remission status. Our findings revealed a significant reduction in plasma and urinary levels of fatty acid-binding protein 5 (FABP5) in SDNS cases during remission, but not observed in SSNS cases. While FABP5 plays a pivotal role in various diseases including metabolism disorders, the major function of FABP5 is to regulate the intracellular levels of fatty acids and specific metabolic pathways. The role of FABP5 in human podocytes was not well defined.

##### **Methods**

To elucidate FABP5's role, we treated immortalized human podocytes with recombinant C5a. We assessed FABP5 activation by detecting its nuclear translocation using immunofluorescence staining and nuclear protein Western blot. To explore FABP's involvement in cellular damage, FABP5 siRNA was used as an inhibitor. ROS and mitochondrial damage were then measured by DCFDA and cytochrome c detection assays, respectively.

##### **Results**

To clarify the effect of C5a on FABP5, recombinant human C5a was treated in human podocytes. Images of immunofluorescence staining demonstrated that FABP5 was nuclear translocation into human podocytes. The results of Western blot also demonstrated the enhancement of FABP5 nuclear translocation in nuclear fraction in C5a-treated human podocytes. By using FABP5 SiRNA, C5a-induced ROS production and mitochondrial damage in podocytes were significantly reduced.

##### **Conclusions**

Our study demonstrated that FABP5 levels are significantly reduced in plasma and urine in SDNS patients during remission. Of note, we also demonstrated that FABP5 activation is involved in C5a-mediated podocytes damage in vitro. These findings suggest that targeting FABP5 could represent a novel therapeutic strategy for SDNS.

**Keywords :** C5a, podocyte, Fatty acid-binding protein 5 (FABP5), Steroid-dependent nephrotic syndrome (SDNS), Reactive Oxygen Species (ROS)

## Oral Communications : Glomerular Diseases (GN)

Abstract Submission No. : APCN20250205

### Single-Cell Transcriptomics Reveals Age-Dependent Transdifferentiation Potential of Glomerular Parietal Epithelial Cells

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#### Abstract

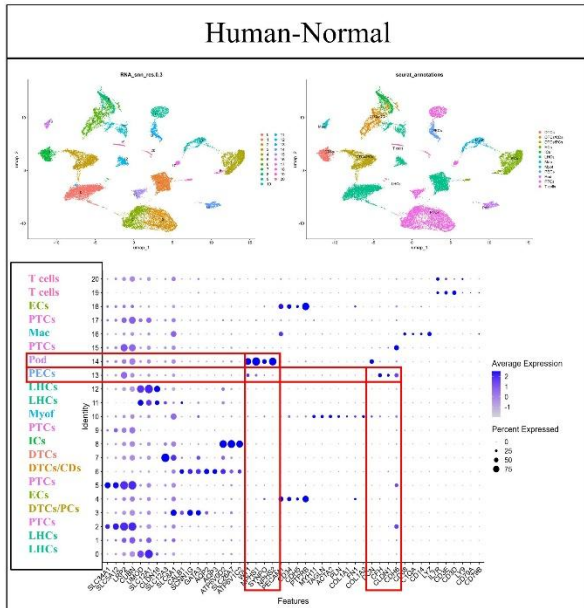
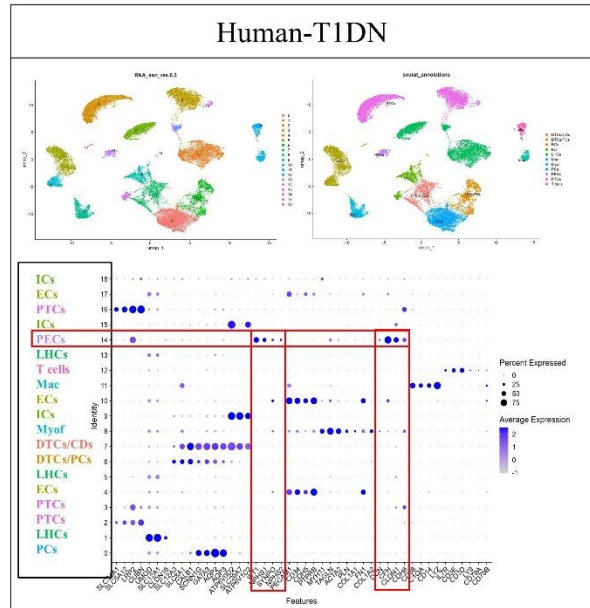
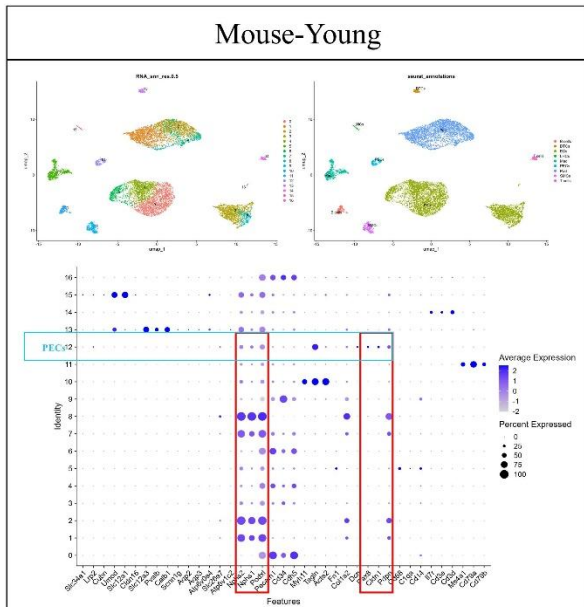
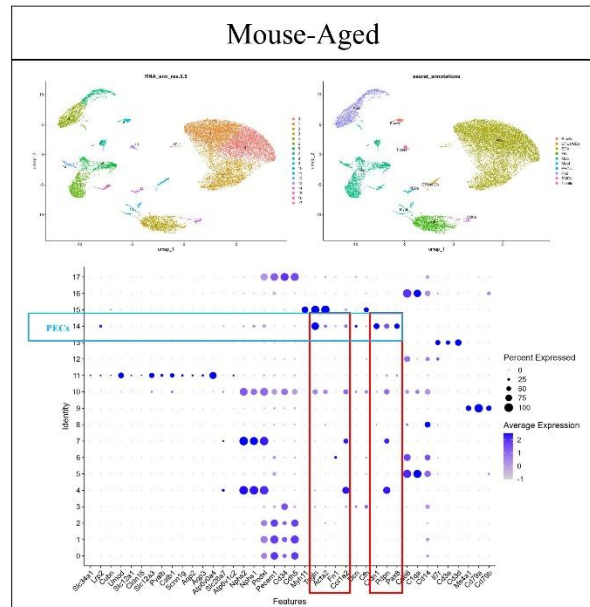
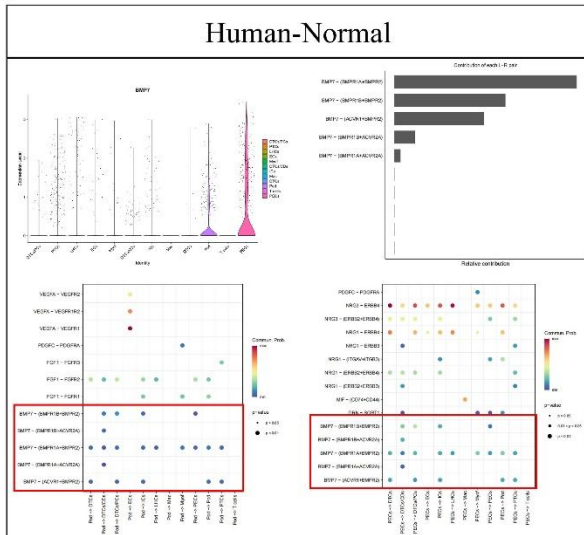
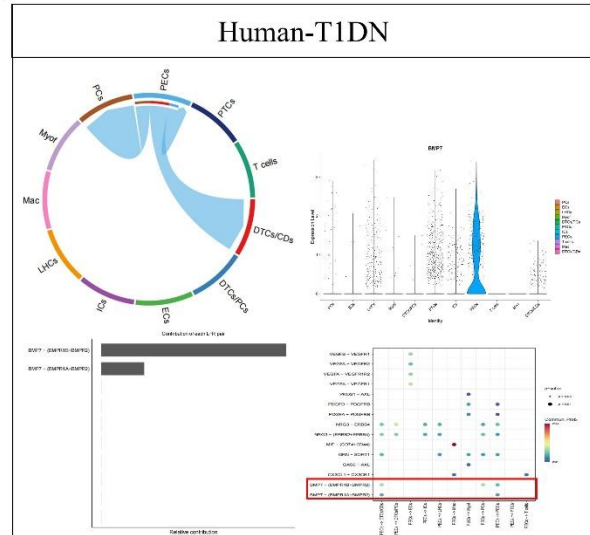
**INTRODUCTION:** Parietal epithelial cells (PECs), lining Bowman's capsule, and podocytes, covering the glomerular basement membrane, are thought to arise from a shared progenitor. In kidney diseases such as focal segmental glomerular sclerosis, crescentic glomerulonephritis, and type 1/2 diabetic nephropathy (T1/2DN), PEC activation and proliferation, alongside podocyte injury and detachment, are key pathological features. However, the potential for PEC-to-podocyte transdifferentiation remains debated. This study investigates the age-dependent transdifferentiation potential of PECs using single-cell RNA sequencing (scRNA-seq) data from both human and murine kidneys.

**METHODS:** We analyzed publicly available scRNA-seq datasets from the Gene Expression Omnibus (GEO) database: GSE240374 (kidneys from 2 young and 2 aged mice) and GSE279086 (kidneys from 10 healthy individuals and 28 patients with T1DN, aged  $24 \pm 3$  years). After quality control and filtering, we integrated the datasets using Harmony and performed dimensionality reduction with PCA and UMAP. Cell clustering was conducted and cell types were manually annotated based on canonical marker genes curated from published literature. Differential gene expression analysis and visualization of lineage-specific markers were performed to examine transdifferentiation signatures. Additionally, intercellular communication was inferred using CellChat to investigate ligand-receptor signaling networks.

**RESULTS:** Firstly, the data showed that podocytes in kidneys from patients with T1DN could not be distinctly clustered compared to those from healthy young individuals. Meanwhile, PECs exhibited significant expression of podocyte-specific markers, suggesting a potential for transdifferentiation into podocytes (Figure 1A, B). Subsequently, in young mouse kidneys, podocytes accounted for 33.02% of total kidney cells, and PECs showed low-level expression of podocyte markers (Figure 1C). In contrast, in aged mouse kidneys, the proportion of podocytes declined to 10.69%, and PECs strongly expressed myofibroblast markers, including *Tagln*, *Acta2*, *Fn1*, and *Coll1a2* (Figure 1D). Finally, in healthy young human kidneys, both PECs and podocytes were identified as major sources of bone morphogenetic protein 7 (BMP7), a key anti-fibrotic and anti-inflammatory cytokine (Figure 1E). In T1DN kidneys, PECs undergoing transdifferentiation into podocytes displayed upregulated BMP7 secretion (Figure 1F).

**CONCLUSION:** Our findings indicate that PECs from young individuals may exert a protective role by transdifferentiating into podocytes and secreting BMP7. In aged kidneys, this reparative capacity is diminished, and instead, PECs contribute to fibrosis by transitioning into myofibroblast-like cells.

**Keywords :** parietal epithelial cell, podocyte, single-cell RNA sequence

**A****B****C****D****E****F**

## Oral Communications : Glomerular Diseases (GN)

Abstract Submission No. : APCN20250497

### Evaluation of hematuria in patients treated with Ravulizumab in the phase 2 SANCTUARY trial

Jonathan Barratt<sup>1</sup>; Jessica Kaufeld<sup>2</sup>; Richard Lafayette<sup>3</sup>; Miguel Giovanni Uriol Rivera<sup>4</sup>; Seung Hyeok Han<sup>5</sup>; Ping-Chin Lai<sup>6</sup>; Nicolas Maillard<sup>7</sup>; Adrian Schreiber<sup>8</sup>; Roberta Fenoglio<sup>9</sup>; Katherine Garlo<sup>10</sup>; Kara Rice<sup>11</sup>; Andreas Kateifides<sup>10</sup>; Youssef MK Farag<sup>10</sup>; Michal Nowicki<sup>12</sup>

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#### Abstract

**Background:** In a phase 2 trial (NCT04564339) in adults with IgA nephropathy (IgAN), ravulizumab (RAV), a complement C5 inhibitor, led to reduction in proteinuria. Hematuria may reflect morphological changes at the glomerular filtration barrier, could be toxic to the tubules, and may be valuable in assessing prognosis and response to treatment. Evaluating hematuria could enhance understanding of the benefits of complement blockade in IgAN.

**Methods:** In this phase 2 trial, patients (pts) were randomized (2:1) to RAV (IV; q8w) or placebo (PBO) for 26 weeks (wks) followed by a 24-wk open-label RAV treatment period. Single void collections for random spot urine samples were used for hematuria evaluation, assessed by examination of the spun urine sediment by microscopy (expressed as red blood cells [RBCs]/high-power field [HPF]). The number of RBCs in urine was summarized by treatment group using frequency statistics for categorical variables. Prespecified analysis included the percentage of pts with <10 RBCs/HPF on urine sediment from spot samples, as reported by the central lab from baseline (BL) to wk 50.

**Results:** In the RAV group, 76.7%, 87.8%, and 90.2%, at BL, wk 26, and wk 50, respectively, had <10 RBCs/HPF (Figure). In the PBO group, 69.6% and 77.3% had <10 RBCs/HPF at BL and wk 26, respectively; at wk 50, following crossover to RAV, 100% had <10 RBCs/HPF.

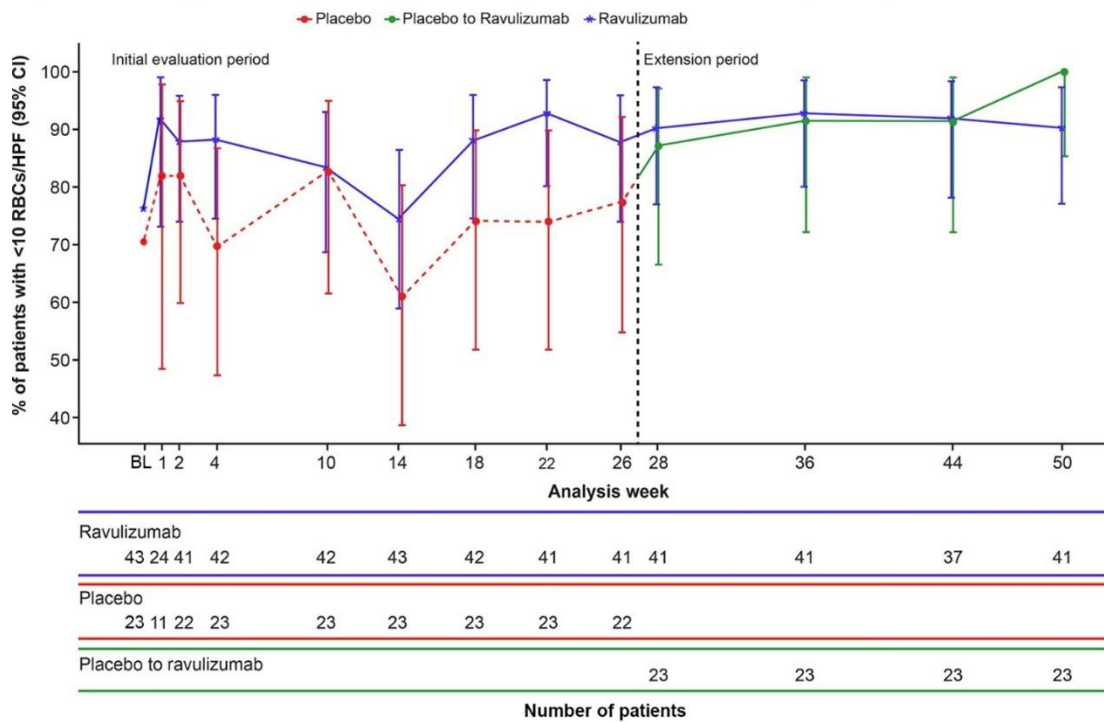
**Conclusion:** A trend in reduction in hematuria with RAV treatment might reflect the anti-inflammatory effect and improved disease control under complement inhibition.

**Funding statement:** Commercial Support - Alexion, AstraZeneca Rare Disease

"This abstract was also submitted for the ASN Kidney Week 2025 congress. By submitting the abstract to APCN x TSN 2025, abstract authors declare that re-submitting the abstract is permitted by the organizers of the previous meeting".

**Keywords :** IgA nephropathy; Complement

**Figure: Percentage of patients with <10 RBCs/HPF on urine sediment from spot samples per central lab**



Black dotted line indicates crossover from placebo to ravulizumab.  
 Confidence intervals not available for baseline data points.  
 BL, baseline; CI, confidence interval; HPF, high-power field; RBC, red blood cell.

## **Oral Communications : Glomerular Diseases (GN)**

**Abstract Submission No. : APCN20250810**

### **Use of immunosuppression in severe paediatric IgA Nephropathy: a multi-national multi-centre study**

Alison Ma<sup>1</sup>; Matko Marlais<sup>2</sup>; Chloe Siu<sup>3</sup>; Lawrence Ma<sup>4</sup>; Kjell Tullus<sup>2</sup>; Eugene Yu-hin Chan<sup>5</sup>;  
On behalf of all co-authors<sup>6</sup>

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<sup>2</sup> Nephrology Department, Great Ormond Street Hospital for Children

<sup>3</sup> Department of Paediatrics and Adolescent Medicine, Hong Kong Children's Hospital

<sup>4</sup> Department of Psychology, The Educational University of Hong Kong

<sup>5</sup> Department of Paediatrics, Chinese University of Hong Kong.

<sup>6</sup> Paediatric IgAN Study Group

#### **Abstract**

##### **Background**

The optimal remission criteria and long-term outcomes for children with severe IgA nephropathy (IgAN) remain unclear. We propose adopting KDIGO criteria for childhood-onset lupus nephritis and IPNA criteria for idiopathic nephrotic syndrome to define remission in nephritic and rapidly progressive glomerulonephritis (RPGN) as well as nephrotic presentations. We explore the applicability of revised remission criteria for severe IgAN and examine the clinical significance of defining partial remission (PR) within this specific patient population.

##### **Method**

This multi-national retrospective cohort study involved 50 tertiary paediatric nephrology centres across 25 countries. We included children with biopsy-proven IgAN treated with immunosuppression for severe presentations, including acute nephritic syndrome/RPGN and nephrotic syndrome. Primary outcome was complete or partial remission (CR/PR). Secondary outcomes included event-free survival from advanced chronic kidney disease (CKD) (stage 3-5D/T).

##### **Results**

We analysed 133 children with severe IgAN (age, 10.2 years [IQR, 7.3-13.4]; 80 boys; nephritic/RPGN, n=75; nephrotic, n=58) treated with immunosuppression. All except four subjects received corticosteroids; 63% received additional immunosuppressants. Renin-angiotensin-aldosterone inhibitors were used in 94%. Median observation period was 55 months (IQR, 34.5-92).

More patients with nephrotic syndrome achieved CR/PR than those with nephritic/ RPGN group at both 6 months (82.5% [95% CI, 69.6-90.8] vs. 76.0% [95% CI, 64.5-84.8]) and 12 months (87.9% [95% CI, 76.1-94.6] vs. 72.0% [95% CI, 60.3-81.5]). Kaplan-Meier analysis indicated nephritic/RPGN presentation had a trend towards worse survival free from advanced CKD (log-rank p=0.09). Multivariable analysis of the entire cohort identified older age at diagnosis (HRadj 1.25, 95% CI, 1.06-1.46 p=0.03), lower baseline eGFR (HRadj 0.97, 95% CI, 0.96-0.09; p=0.006), 6-months PR (HRadj 5.45, 95% CI, 1.10-27.02; p=0.04) and non-remission (HRadj 12.52, 95% CI, 2.73-57.56, p=0.001) as independent predictors of advanced CKD. Patients achieving CR under both IPNA IgAN criteria and the proposed criteria demonstrated comparable kidney outcomes.

##### **Conclusions**

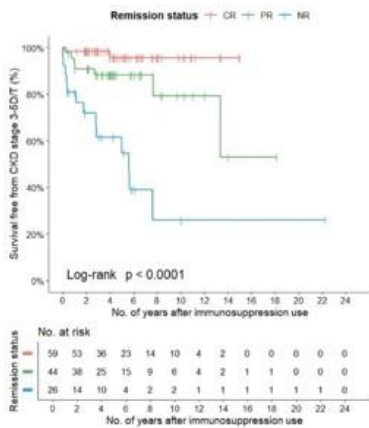
While a subset of severe paediatric IgAN achieve remission following immunosuppression, nephritic/RPGN and nephrotic presentations differ clinically, and a significant proportion of children de-

velop advanced CKD. The proposed remission criteria correlate with long-term kidney outcomes. We highlight the rationale for considering PR, as it defines a subgroup of patients with an intermediate clinical evolution between CR and NR, potentially guiding more tailored therapeutic approaches.

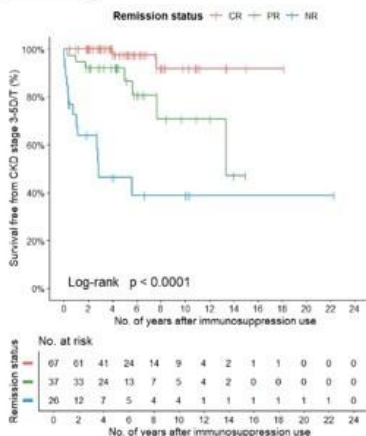
**Keywords :** IgA nephropathy, immunosuppression, corticosteroids, children, nephrotic syndrome, rapidly progressive glomerulonephritis.

**Figure 1. Survival free from advanced CKD stage 3-5D/T based on remission status as defined by the proposed criteria at A) 6- and B) 12-months after immunosuppression use ; IPNA IgAN criteria for C) 6 months after Immunosuppression (CR, complete remission; PR, partial remission; NR, non-remission)**

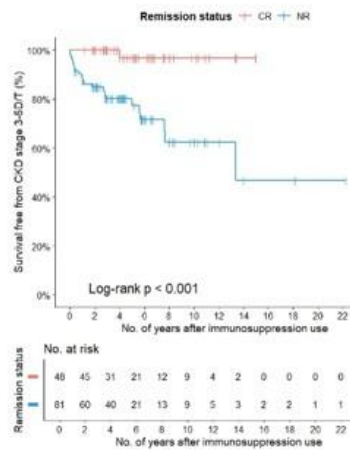
**A (6-months, proposed criteria)**



**B (12-months, proposed criteria)**



**C (6-months, IPNA criteria)**



## Oral Communications : Glomerular Diseases (GN)

Abstract Submission No. : APCN20250777

### Longer Follow-Up of Povetacept Shows Potential for Treatment of IgA Nephropathy (RUBY-3 Study)

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

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<sup>2</sup> Central Florida Kidney Specialists, Orlando, FL, USA

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<sup>4</sup> Seoul National University Hospital, Seoul, Republic of Korea

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<sup>6</sup> Ajou University School of Medicine, Suwon-si, Republic of Korea

<sup>7</sup> Kyung Hee University Hospital at Gangdong, Seoul, Republic of Korea

<sup>8</sup> Vertex Pharmaceuticals, Boston, MA, USA

<sup>9</sup> NephroNet Clinical Trials Consortium and Emory University School of Medicine, Atlanta, GA, USA

<sup>10</sup> Hallym University Sacred Heart Hospital, Anyang-si, Republic of Korea

#### Abstract

**Introduction:** The pathogenesis of IgAN is due to genetic and environmental factors that prime B-cells to express Gd-IgA1, an auto-antigen, triggering autoantibody production, forming immune complexes that deposit in glomerular mesangium, leading to inflammation and injury. BAFF and APRIL are involved in survival and maturation of transitional and naïve B cells, T cell-independent B-cell responses to certain antigens, B-cell regulation, and Ig class-switch recombination. Povetacept, a dual inhibitor of BAFF and APRIL, represents significant therapeutic advancement by targeting the root cause of IgAN. Updated interim data for participants dosed with povetacept in the RUBY-3 study are provided and longer-term data will be provided in the presentation.

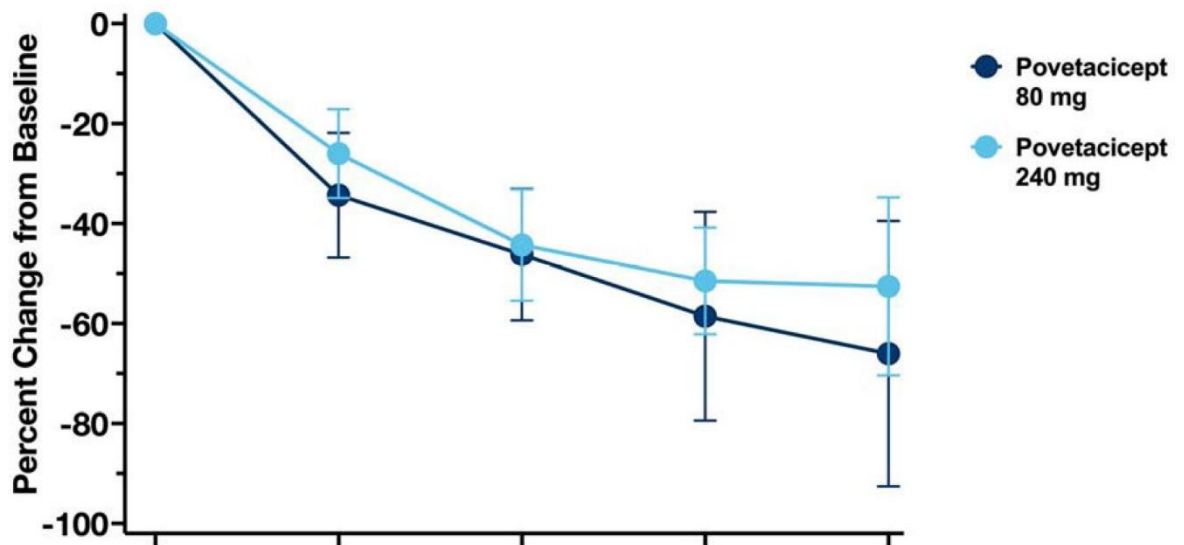
**Methods:** RUBY-3 is an ongoing Phase 1/2, open-label study in adults with IgAN, receiving povetacept 80 mg (n=21 dosed; n=8 at 48 weeks) or 240 mg (n=33 dosed; n=12 at 48 weeks) subcutaneously Q4W. Primary objective: evaluation of the safety of povetacept. Secondary objectives: **efficacy, PK, and biomarker changes with povetacept treatment.**

**Results:** Data at 48 weeks indicate mean 24-hour UPCR decreased 66% from baseline (from 1.3g/g to 0.5g/g) in the 80 mg cohort, and 53% (from 1.2g/g to 0.6g/g) in the 240mg cohort. In both cohorts, eGFR was stable through 48 Weeks. By Week 48, clinical remission was achieved by 63% of the 80 mg cohort and 33% of the 240 mg cohort. Gd-IgA1 declined 64% in the 80 mg cohort and 60% in the 240 mg cohort by Week 24, with sustained declines through Week 44. Povetacept doses were generally safe and well tolerated at both dose levels.

**Conclusion:** Povetacept was generally safe and well tolerated in adults with IgAN and resulted in substantial and sustained reductions in UPCR and Gd-IgA1, with stable eGFR, through 48 weeks. These updated data reinforce the potential of povetacept as therapy for IgAN; a Phase 3 randomized, controlled study of povetacept in IgAN is well underway.

**Keywords :** IgAN, immunoglobulin A nephropathy, povetacept, RUBY-3, best-in-class, UPCR, Gd-IgA1, eGFR

RUBY-3 Study, 24-hour UPCR Mean Percent Change from Baseline to Week 48



Week	BL	W12	W24	W36	W48
80 mg (N)	21	20	18	9	8
240 mg (N)	33	33	31	26	12

## Oral Communications : Glomerular Diseases (GN)

Abstract Submission No. : APCN20250597

### Impact of endocapillary proliferation and membranous histology on patient outcomes among Southeast Asians with lupus nephritis

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#### Abstract

**Aim:** Lupus nephritis has a relapsing/remitting course that can progress to kidney failure. This study aims to assess the impact of histological classes on patient outcomes among multi-racial Southeast Asians treated for lupus nephritis.

**Method:** We performed a single-center, retrospective cohort study of adults with biopsy-proven lupus nephritis diagnosed between 2015 and 2022 with complete histology and follow-up data. Kidney histology was categorized based on presence of focal or diffuse endocapillary proliferation, membranous changes or both. The outcome was the development of kidney failure and/or death during follow-up until death or last visit or 15th August 2024, whichever was earlier. Kaplan Meier survival curves were used to describe the development of the outcome. Associations between histology and the outcomes were assessed using multivariable Cox proportional hazards regression models, accounting for age, sex and kidney function at diagnosis.

**Results:** Among 169 patients with biopsy-proven lupus nephritis (18.3% male), the median age was 43.8 (interquartile range; IQR: 31.8, 55.3) years, serum creatinine was 60 (IQR: 47, 88)  $\mu\text{mol/L}$ , estimated glomerular filtration rate (eGFR) was 104.6 (70.8, 121.5)  $\text{ml/min/1.73 m}^2$  and urine protein-to-creatinine ratio (UPCR) was 2.70 (1.22, 5.16)  $\text{g/g}$ . Half (54.4%) had pre-existing SLE. Histologically, 43.2% had focal endocapillary proliferation, 31.4% had diffuse endocapillary proliferation, 29.0% had membranous component (with or without endocapillary proliferation), whereas 9.5% had isolated membranous nephropathy and 17.8% had mixed endocapillary proliferation and membranous changes.

The median follow-up was 43 (31, 66) months. The outcome occurred in 28 patients (16.6%) at a median of 29 (8, 65) months post-biopsy: 18 had kidney failure (10.7%) and 16 died (9.5%) due to infection (8 patients), cardiovascular disease (2 patients), other or unknown causes (6 patients).

Figure 1 shows that kidney and patient survival tended to be lower in the group with diffuse endocapillary proliferation than the group without (log rank  $p=0.06$ ), with separation of the curves after 5 years. The adjusted HR was 2.11 (95% CI: 0.98, 4.53).

Table 1 shows that focal endocapillary proliferation, membranous component, mixed endocapillary proliferation and membranous changes and isolated membranous histology were not significantly associated with the outcome of kidney failure and/or death in univariable analysis and when adjusted for age and sex.

**Conclusions:** There is a need for further studies to investigate the importance of histological classes on lupus nephritis prognosis and patient outcomes.

**Keywords :** Lupus Nephritis

Figure 1. Kaplan Meier curve for time to kidney failure and/or death comparing the group with diffuse proliferative endocapillary proliferation (red line) and without (blue line), log rank p=0.06.

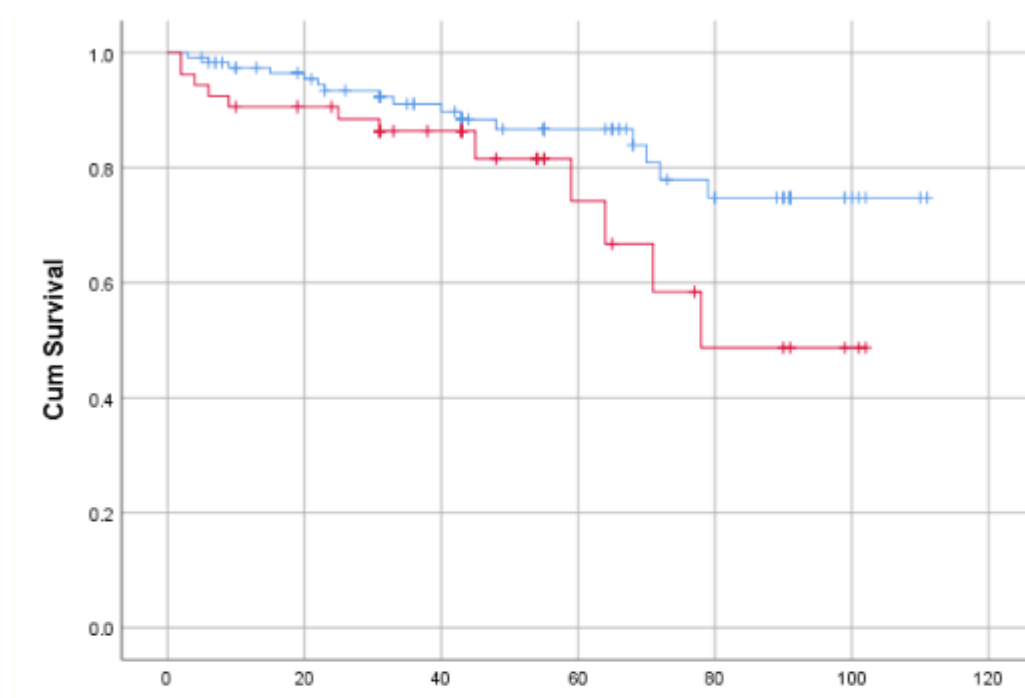


Table 1. Cox regression analysis for the association between histology (with and without other factors) and kidney failure and/or death.

	Model 1 Univariable HR (95% CI)	Model 2 Multivariable HR (95% CI)
Focal endocapillary proliferation, yes versus no	0.81 (0.38, 1.74)	0.69 (0.32, 1.49)
Diffuse endocapillary proliferation, yes versus no	2.00 (0.94, 4.25)	2.11 (0.98, 4.53)
Membranous, yes versus no	0.61 (0.26, 1.44)	0.53 (0.22, 1.27)
Isolated membranous, yes versus no	0.26 (0.04, 1.92)	0.32 (0.04, 2.41)
Mixed endocapillary proliferation and membranous, yes versus no	1.07 (0.43, 2.64)	0.80 (0.31, 2.05)
HR, hazards ratio; CI, confidence interval		
Model 1: histology alone (complete case analysis, n = 169, events = 28)		
Model 2: histology + age + sex (complete case analysis, n = 169, events = 28)		

## Oral Communications : Glomerular Diseases (GN)

Abstract Submission No. : APCN20250489

### Efficacy of Ravulizumab on Proteinuria Response by Baseline Proteinuria or eGFR: A post hoc analysis of the SANCTUARY trial

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#### Abstract

**Background:** In this phase 2 randomized controlled double-blind trial (NCT04564339), adults with IgA nephropathy (IgAN) received the complement C5 inhibitor ravulizumab (RAV) (IV; q8w) or placebo (PBO) for the first 26 weeks (wk). Early and clinically meaningful reduction in proteinuria was observed. Here, we evaluate whether this benefit was independent of baseline (BL) proteinuria or estimated glomerular filtration rate (eGFR) at baseline (BL).

**Methods:** A post-hoc analysis assessed the impact of BL proteinuria and eGFR on treatment effect of RAV on proteinuria at wk26. A mixed model for repeated measures was used to analyze the change from BL in log-transformed spot urine protein-to-creatinine ratio (UPCR) including an interaction term for either treatment group by BL spot UPCR or treatment group by BL eGFR.

**Results:** In the primary model without the interaction term, wk26 UPCR reduction was -38.1% (95% CI: -48.3%, -26.0%) for RAV vs -15.3% (-34.0%, 8.8%) for PBO. In the model with treatment by BL spot UPCR interaction, reduction was similar: -38.2% (-48.3%, -26.0%) for RAV and -15.3% (-34.0%, 8.8%) for PBO. For each 1-point increase in BL spot UPCR, there was a non-significant increase of 8% in the treatment effect (interaction coefficient=0.92, P=0.6; Fig 1). Similarly, in the model with treatment by BL eGFR interaction, reduction was similar and the interaction was non-significant (interaction coefficient=0.00; P=0.8; Fig 2).

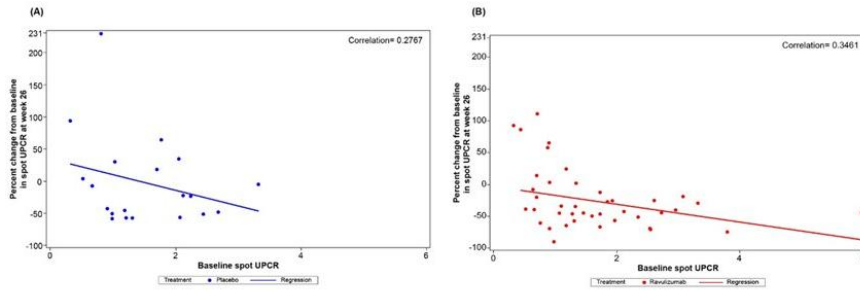
**Conclusion:** In this post-hoc analysis, BL proteinuria and eGFR did not significantly modify the treatment effect of RAV on proteinuria at wk26, suggesting that RAV reduces proteinuria across a range of disease severity at treatment initiation.

**Funding statement:** Commercial Support - Alexion, AstraZeneca Rare Disease

This abstract was also submitted for the ASN Kidney Week 2025 congress. By submitting the abstract to APCN x TSN 2025, abstract authors declare that re-submitting the abstract is permitted by the organizers of the previous meeting

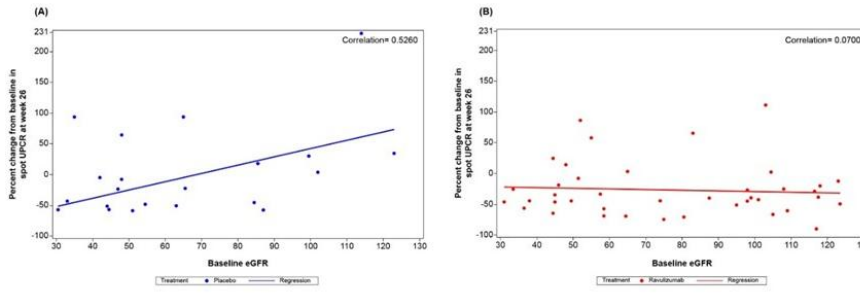
**Keywords :** IgA nephropathy; Complement; Clinical trial

Fig. 1. Spot UPCR reduction at wk26 by continuous BL spot UPCR: (A) Placebo (B) Ravulizumab



Note: This analysis uses spot UPCR collections at baseline, while study eligibility was based on 24-hour absolute urine protein and from collections that could have been completed anytime within the 6 weeks prior to Day 1.

Fig. 2. Spot UPCR reduction at wk26 by continuous BL eGFR: (A) Placebo (B) Ravulizumab



## Oral Communications : Glomerular Diseases (GN)

Abstract Submission No. : APCN20251025

### Change in soluble biomarker levels in patients with IgA nephropathy: an analysis of the phase 2 trial of ravulizumab (SANCTUARY)

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#### Abstract

##### Background:

Complement activation plays an important role in the pathophysiology of IgA nephropathy (IgAN), leading to inflammation and progressive kidney damage. In a phase 2 trial, clinically meaningful proteinuria reduction was observed with the complement C5 inhibitor, ravulizumab (RAV).<sup>1</sup> Here, we evaluated change over time in soluble biomarkers in patients (pts) treated with RAV vs placebo (PBO).

##### Methods:

In SANCTUARY (NCT04564339), 66 adults with IgAN were randomized (2:1) to RAV (IV q8w) or placebo (PBO) for 26 weeks (wks). Spot urine was collected pre-dose on days 1, 15, 71, 127, and 183. Evaluable data were available from 60 pts. Validated immunoassays were performed on spot urine and soluble biomarker levels were normalized to urine creatinine (Cr). Longitudinal changes in biomarker levels were reported using descriptive statistics and a mixed model for repeated measures (MMRM) to compare RAV with PBO.

##### Results:

With RAV, there was early (by Day 15), sustained, and marked reduction in sC5b-9/Cr and Ba/Cr (complement pathway products) (Figure). Sustained reduction in CD163/Cr (macrophage renal infiltration marker) was observed starting at day 71. MMRM analysis of change from baseline to wk26 showed significant reduction in sC5b-9/Cr, Ba/Cr, CD163/Cr, and KIM-1/Cr (proximal tubule injury marker) with RAV vs PBO (Figure).

##### Conclusion:

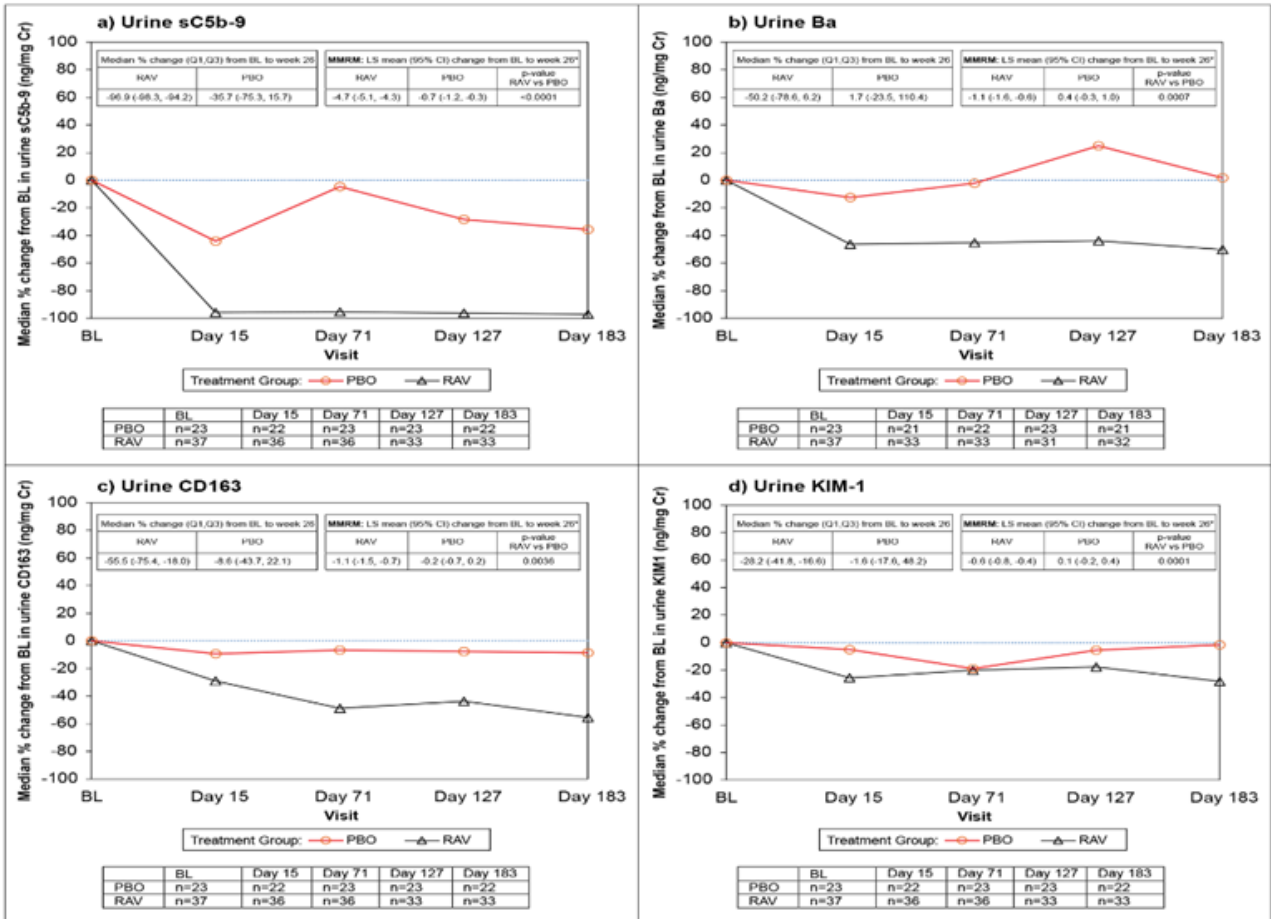
In pts treated with RAV, there was an early and sustained reduction in biomarkers of complement activation and reduction in markers of macrophage renal infiltration and tubular injury. These results suggest reduced inflammation and kidney damage in response to C5 (terminal complement) inhibition and are consistent with the observed proteinuria reduction in SANCTUARY.<sup>1</sup>

1. Lafayette R, et al. J Am Soc Nephrol. 2025;36(4):645–656.

“This abstract was also submitted for the ASN Kidney Week 2025 congress. By submitting the abstract to APCN x TSN 2025, abstract authors declare that re-submitting the abstract is permitted by the organizers of the previous meeting”.

**Keywords :** IgA nephropathy; Complement; Clinical trial

Figure: Change in biomarker levels with ravulizumab vs placebo



\*LS mean change from baseline values are based on an MMRM model that includes log(2) of change from baseline as the dependent variable, includes the fixed, categorical effects of visit, treatment group, and randomization stratification factor, treatment group by visit interaction, and continuous effect of the log(2) of baseline value as covariate.