Oral 5-5

Evaluation of Hematuria in Patients Treated with Ravulizumab in the Phase 2 SANCTUARY Trial

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Introduction

- In the phase 2 **SANCTUARY** trial (NCT04564339) in adults with IgA nephropathy, rapid and clinically meaningful **reduction in proteinuria** was observed with **ravulizumab** treatment versus **placebo**[1]
- Ravulizumab is a potent, second-generation **inhibitor of complement C5** that prevents the formation of the terminal pathway C5a anaphylatoxin and C5b-9 membrane attack complex[1,2]
- Complement activation, which culminates in the terminal pathway, plays a central role in IgA nephropathy, triggering inflammation, production of extracellular matrix, cellular apoptosis, and damaging the glomerular filtration barrier[2]
- **Hematuria** is a readily available and **informative clinical marker** of disease activity in **IgA nephropathy**[3]
- 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[3,4]
- Evaluating hematuria could enhance understanding of the benefit of complement blockade in IgA nephropathy

Objectives

- **Prespecified analysis:** To evaluate the **percentage of patients** with **<10 RBCs/HPF** on urine sediment from spot samples, as reported by the central laboratory, from baseline to Week 50
- ***Post hoc* analysis:** To evaluate the **percentage of patients** with **≤5 RBCs/HPF** on urine sediment from spot samples, as reported by the central laboratory, from baseline to Week 50

HPF, high-power field; IgA, immunoglobulin A; RBCs, red blood cells.

1. Lafayette R, et al. *J Am Soc Nephrol*. 2025;36(4):645-656; **2.** Duval A.. et al. *Nephrol Dial Transplant*. 2023;38(12):2685-2693; **3.** Zand L, et al. *Clin Kidney J*. 2023;16(Suppl 2):ii19-ii27; **4.** Saha MK, et al. *Am J Kidney Dis*. 2022;80(3):383-392.

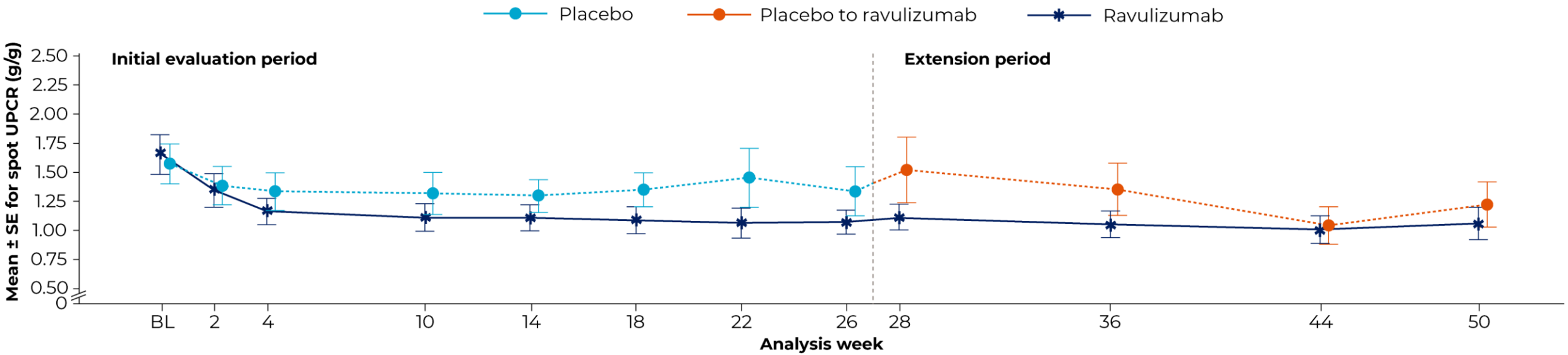
Methods

- In this phase 2 trial, N=66 patients were randomized (2:1) to **ravulizumab** (IV; q8w) or **placebo** for 26 Weeks, followed by a 24-week open-label ravulizumab treatment period
  - Randomization was stratified by mean proteinuria (1 to 2 g/day versus >2 g/day) based on 2 valid 24-hour urine collections during the screening period
- **Key inclusion criteria**
  - Patients aged 18-75 years with biopsy-proven IgA nephropathy
  - Mean proteinuria ≥1.0 g/day on two complete and valid 24-hour urine collections during the screening period and adherence to a stable and optimal dose of RAAS inhibition
  - eGFR ≥30 mL/min/1.73 m^2
- 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 RBCs/HPF)
- The number of RBCs in urine were summarized at each time point by treatment group using frequency statistics for categorical variables

eGFR, estimated glomerular filtration rate; HPF, high-power field; IgA, immunoglobulin A; IV, intravenous; q8w, every 8 Weeks; RAAS, renin-angiotensin-aldosterone system; RBCs, red blood cells.

Results: Mean Spot UPCR Assessment over 50 Weeks

Proteinuria (spot UPCR) reduction: exploratory endpoint in SANCTUARY trial[1*]



Number of patients												
Ravulizumab	43	41	43	43	43	41	41	40	42	40	40	39
Placebo	22	22	22	21	22	21	22	20				
Placebo to ravulizumab									22	22	22	22

[*] Note: Black dotted line indicates crossover from placebo to ravulizumab.

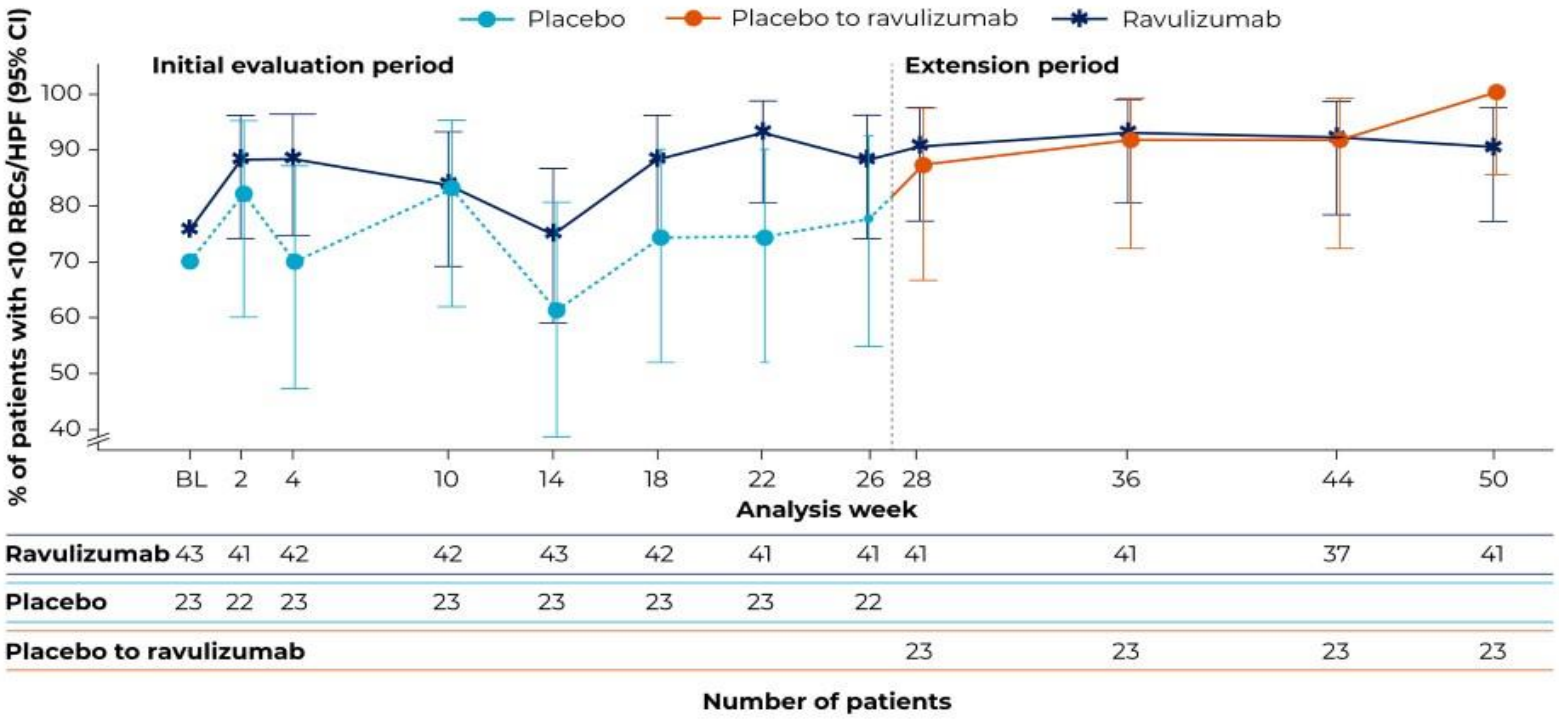
SE, standard error; UPCR, urine protein-creatinine ratio.

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

Results: Prespecified Exploratory Analysis (1/2)

- In the **ravulizumab** group, 76.7%, **87.8%**, and **90.2%** of patients had **<10 RBCs/HPF** at baseline, **Week 26**, and **Week 50**, respectively
- While in the **placebo** group, 69.6% and **77.3%** of patients had <10 RBCs/HPF at baseline and **Week 26**
- At Week 50, following placebo crossover to ravulizumab, 100% of patients had <10 RBCs/HPF

Percentage of patients with <10 RBCs/HPF*



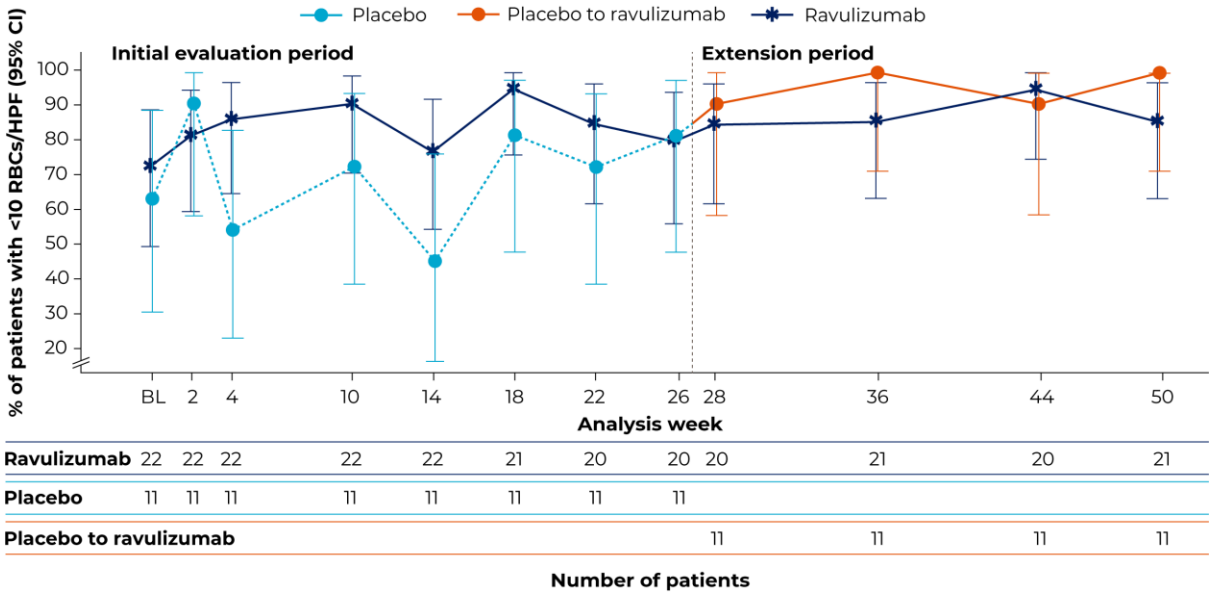
* Note: Black dotted line indicates crossover from placebo to ravulizumab. Confidence intervals not available for baseline data points.

CI, confidence interval; HPF, high-power field; RBCs, red blood cells.

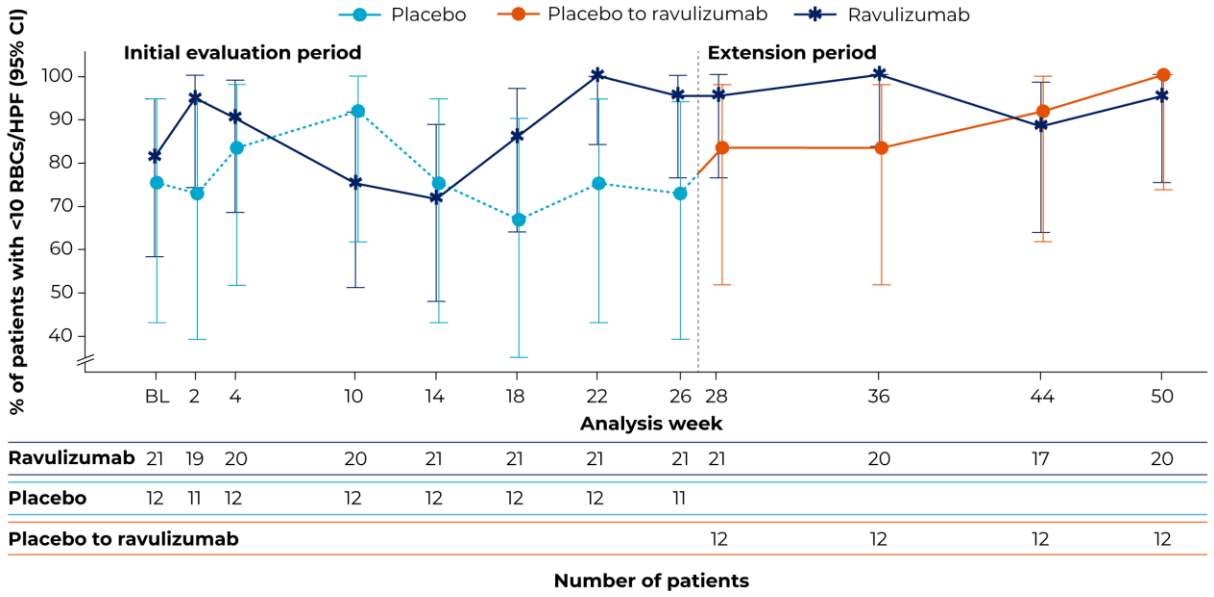
Results: Prespecified Exploratory Analysis (2/2)

- Percentage of patients with **<10 RBCs** in urine by **baseline proteinuria**, 1 to 2 g/day and >2 g/day are shown below; **trends** were **similar** within **subgroups** of baseline proteinuria

Percentage of patients with <10 RBCs/HPF in urine by baseline proteinuria 1 to 2 g/day 24-hour UP*



Percentage of patients with <10 RBCs/HPF in urine by baseline proteinuria >2 g/day 24-hour UP*



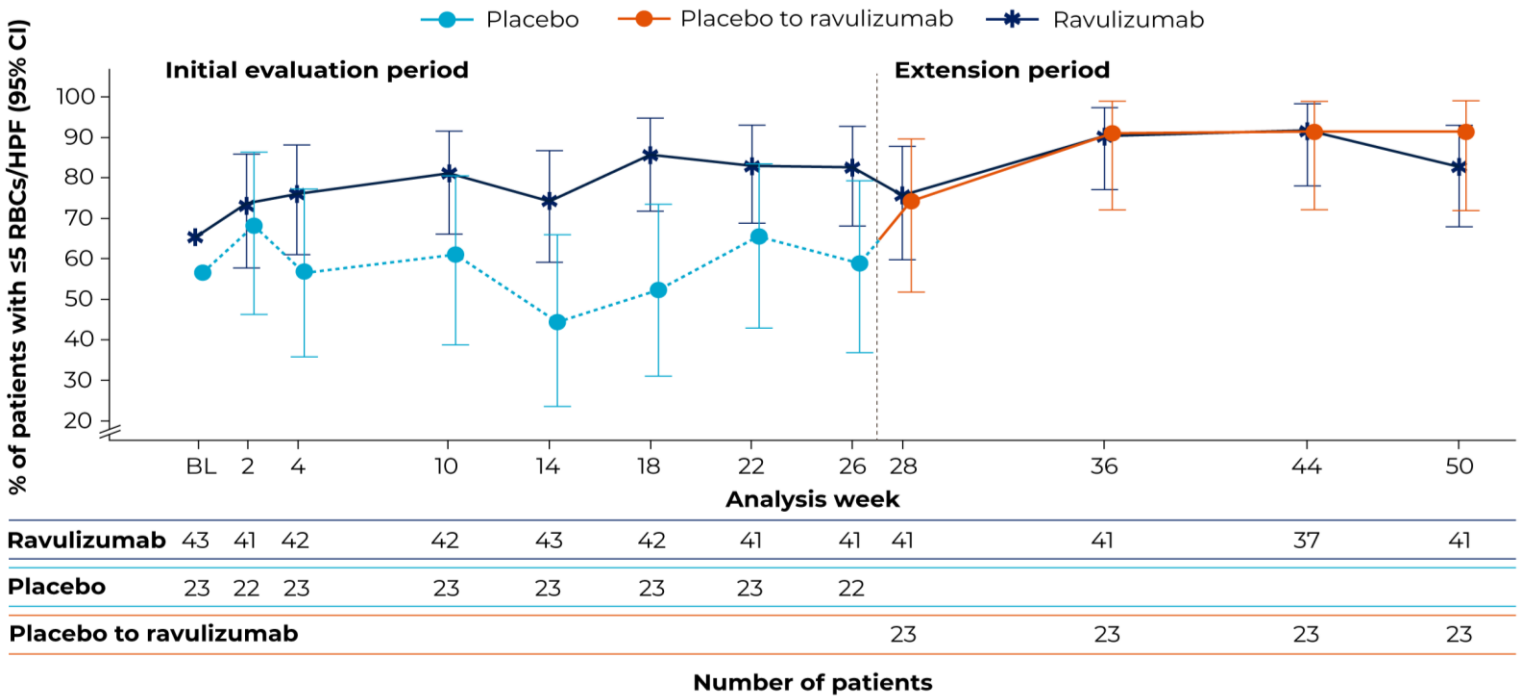
*Note: Black dotted line indicates crossover from placebo to ravulizumab.

CI, confidence interval; HPF, high-power field; RBCs, red blood cells; UP, urine protein.

Results: *Post hoc* Analysis (1/2)

- In the **ravulizumab** group, 65.1%, **82.9%**, and **82.9%** of patients had **≤5 RBCs/HPF** at baseline, **Week 26**, and **Week 50**, respectively
- While in the **placebo** group, 56.5% and **59.1%** of patients had ≤5 RBCs/HPF at baseline and **Week 26**
- At Week 50, following placebo crossover to ravulizumab, 91.3% of patients had ≤5 RBCs/HPF

Percentage of patients with ≤5 RBCs/HPF*



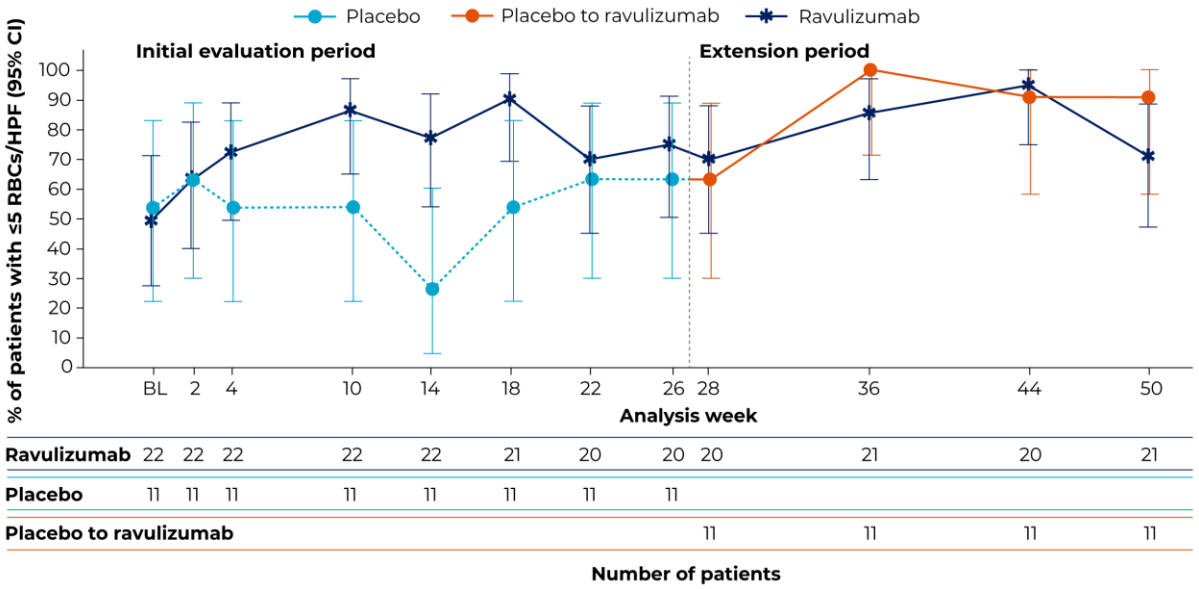
*Note: Black dotted line indicates crossover from placebo to ravulizumab. Confidence intervals not available for baseline data points.

CI, confidence interval; HPF, high-power field; RBCs, red blood cells.

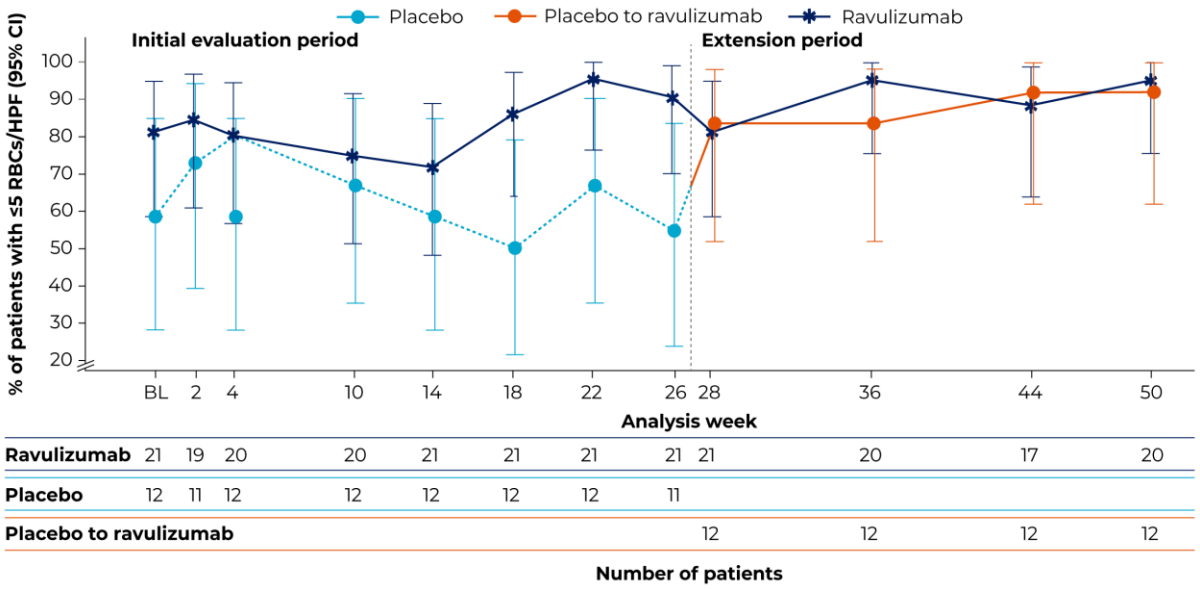
Results: *Post hoc* Analysis (2/2)

- Percentage of patients with **≤5 RBCs** in urine by **baseline proteinuria**, 1 to 2 g/day and >2 g/day are shown below; **trends** were **similar** within **subgroups** of baseline proteinuria

Percentage of patients with ≤5 RBCs/HPF in urine by baseline proteinuria: 1 to 2 g/day 24-hour UP*



Percentage of patients with ≤5 RBCs/HPF in urine by baseline proteinuria: >2 g/day 24-hour UP*



*Note: Black dotted line indicates crossover from placebo to ravulizumab.

CI, confidence interval; HPF, high-power field; RBCs, red blood cells; UP, urine protein.

Conclusions

- The **trend in reduction in hematuria** with ravulizumab treatment might reflect the **anti-inflammatory effect** and resultant **improvement in glomerular filtration** barrier architecture, function, and **overall disease control** under terminal complement inhibition
- **Reduction in hematuria** is **consistent** with the reduction in **proteinuria** observed in the **SANCTUARY** trial

The data were previously presented at the American Society of Nephrology (ASN) Kidney Week 2025, Houston, Texas, United States, November 5–9, 2025.