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Change in Soluble Biomarker Levels in Patients with IgA Nephropathy: An Analysis of the Phase 2 Trial of Ravulizumab (SANCTUARY)

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Background

- **IgA nephropathy** is the most prevalent form of primary glomerulonephritis globally and a leading cause of chronic kidney disease[1,2]
- Activation of the complement system plays a central role in the pathophysiology of IgA nephropathy, leading to terminal complement pathway-mediated inflammation, cellular injury, progressive kidney damage, and nephron loss
    - **Complement activation** leads to glomerular and tubular damage, resulting in proteinuria and contributing to glomerular and tubulointerstitial fibrosis[3-6]
- In a phase 2 RCT of the terminal complement C5 inhibitor **ravulizumab**, a statistically significant and clinically meaningful reduction in proteinuria at Week 26 (30.1% treatment effect vs placebo; P=0.005) was observed, as well as a trend towards stabilization of eGFR[7]
    - Ravulizumab is a second generation **C5 inhibitor** providing immediate, complete and sustained inhibition of terminal complement[7]

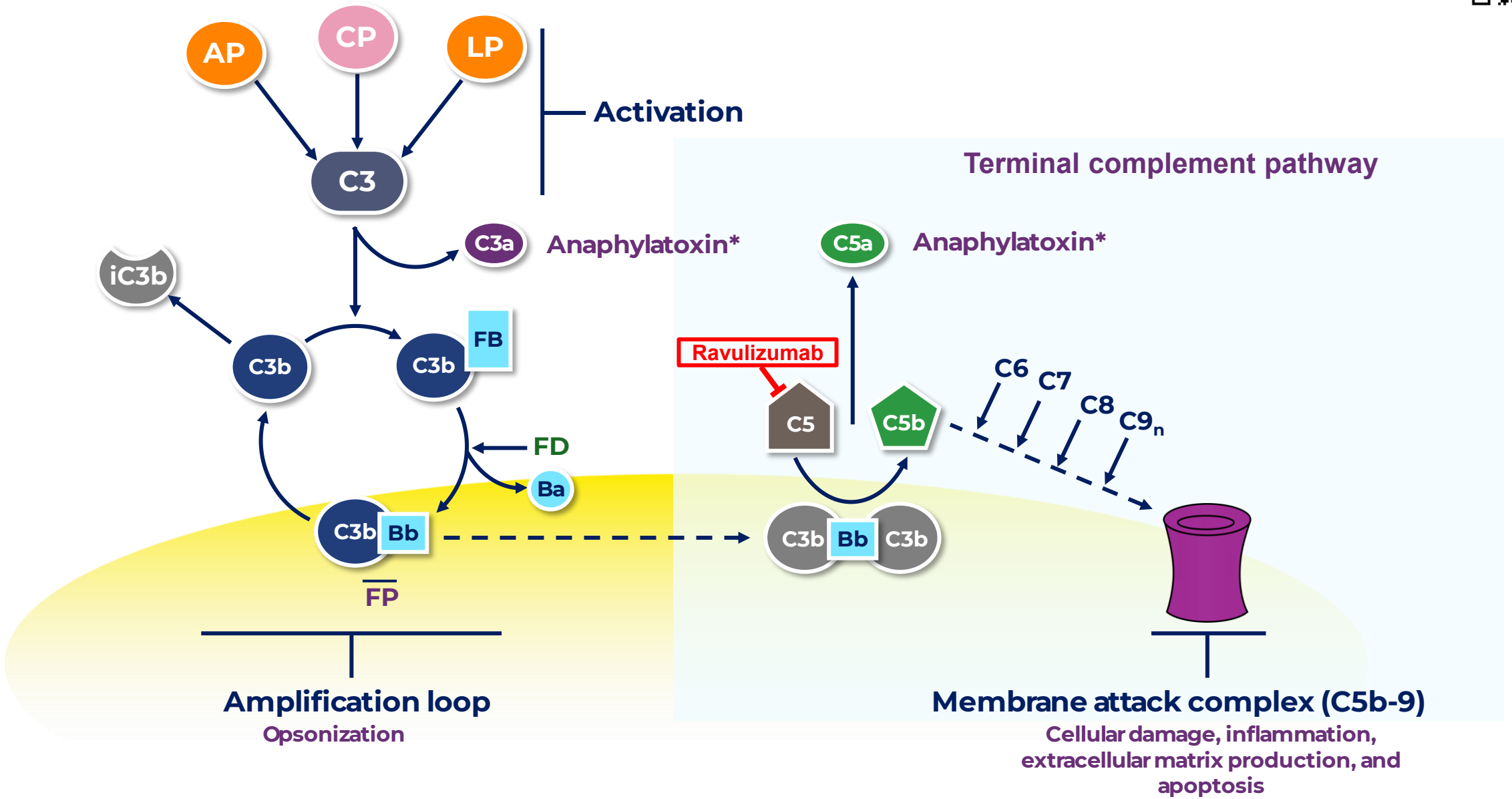
Objective

- To report the **change in urinary biomarkers over time**, among patients with **IgA nephropathy** treated with ravulizumab vs placebo in the **phase 2 SANCTUARY** (NCT04564339) randomized, double-blind, placebo-controlled trial

3 eGFR, estimated glomerular filtration rate; IgA, immunoglobulin; RCT, randomized controlled trial.

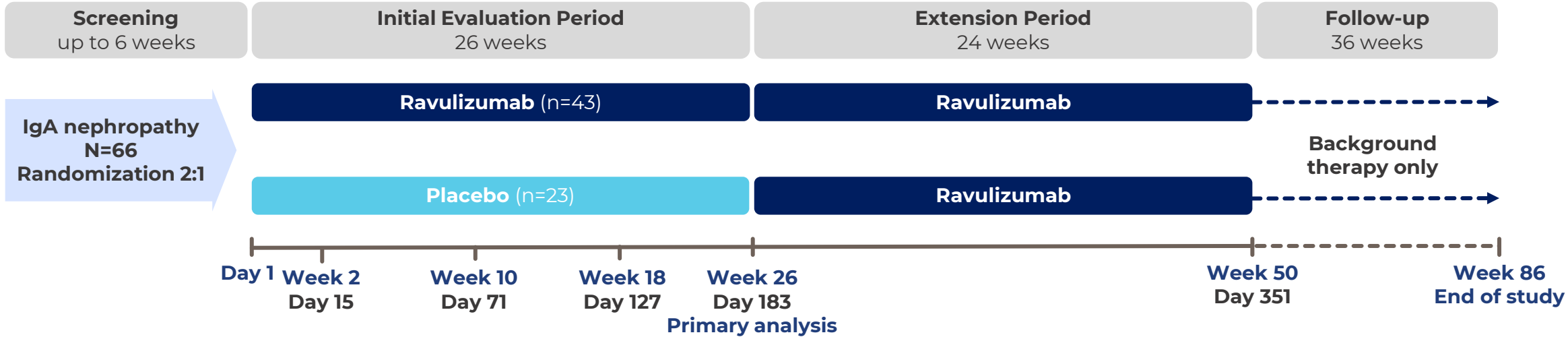
1. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int.* 2021;100(4S):S1–S276; **2.** KDIGO 2025 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV). *Kidney Int.* 2025;108(4S):S1–S71; **3.** Duval A, et al. *Nephrol Dial Transplant.* 2023;30;38(12):2685-2693; **4.** Floege J, et al. *Kidney Int.* 2025;107(4):640–651; **5.** Boor P, et al. *J Am Soc Nephrol.* 2007;18(5):1508-1515; **6.** Abe K, et al. *Clin Exp Immunol.* 2004;136(1):60-66; **7.** Lafayette R, et al. *J Am Soc Nephrol.* 2025;36(4):645–656.

Simplified Schematic of Complement System



4 *triggers inflammation, platelet and neutrophil activation and profibrotic factor.
Figure adapted from Parente R, et al. *Cell Mol Life Sci.* 2017; 74(9):1605-1624.
AP, alternative pathway; CP, classical pathway; C3bBb, C3 convertase; C3bBbC3b, C5 convertase; FB, factor B; FD, factor D; FP, factor P; iC3b, inactive C3b; LP, lectin pathway.

Methods: Biomarker Analyses



Urinary biomarkers assessed in normal donors and patients with IgA nephropathy

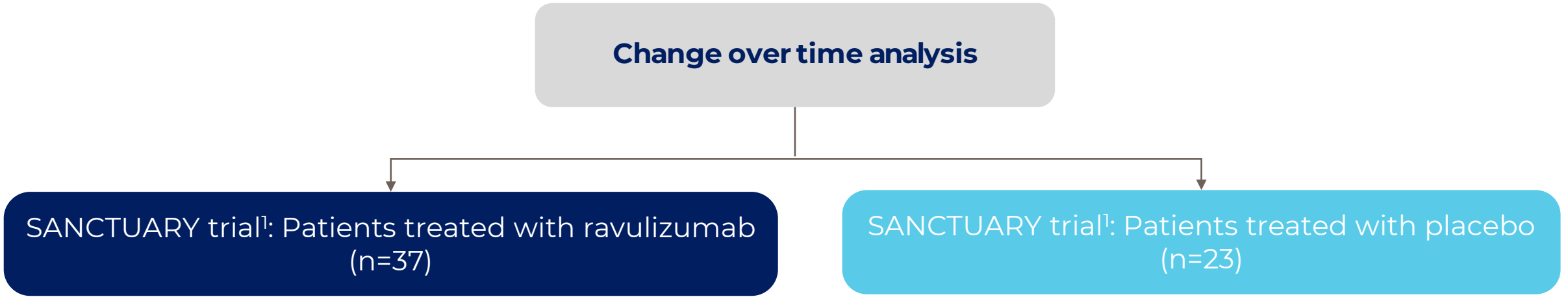
sC5b-9	Factor Ba	CD163	KIM-1	NGAL
(marker of complement activation)	(marker of complement activation)	(marker of macrophage renal infiltration)	(specific marker of renal proximal tubule injury)	(marker of renal tubule injury)

Ligand-binding assays were developed and validated to FDA guidance (Bioanalytical Method Validation, 2018)[1]

Ba, complement factor Ba; CD163, cluster of differentiation 163; IgA, immunoglobulin A; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated lipocalin; sC5b-9, soluble membrane attack complex.

1. Cammett et al. *Mol Diagn Ther.* 2023 Jan;27(1):61-74.

Methods: Biomarker Analyses - Change Over Time



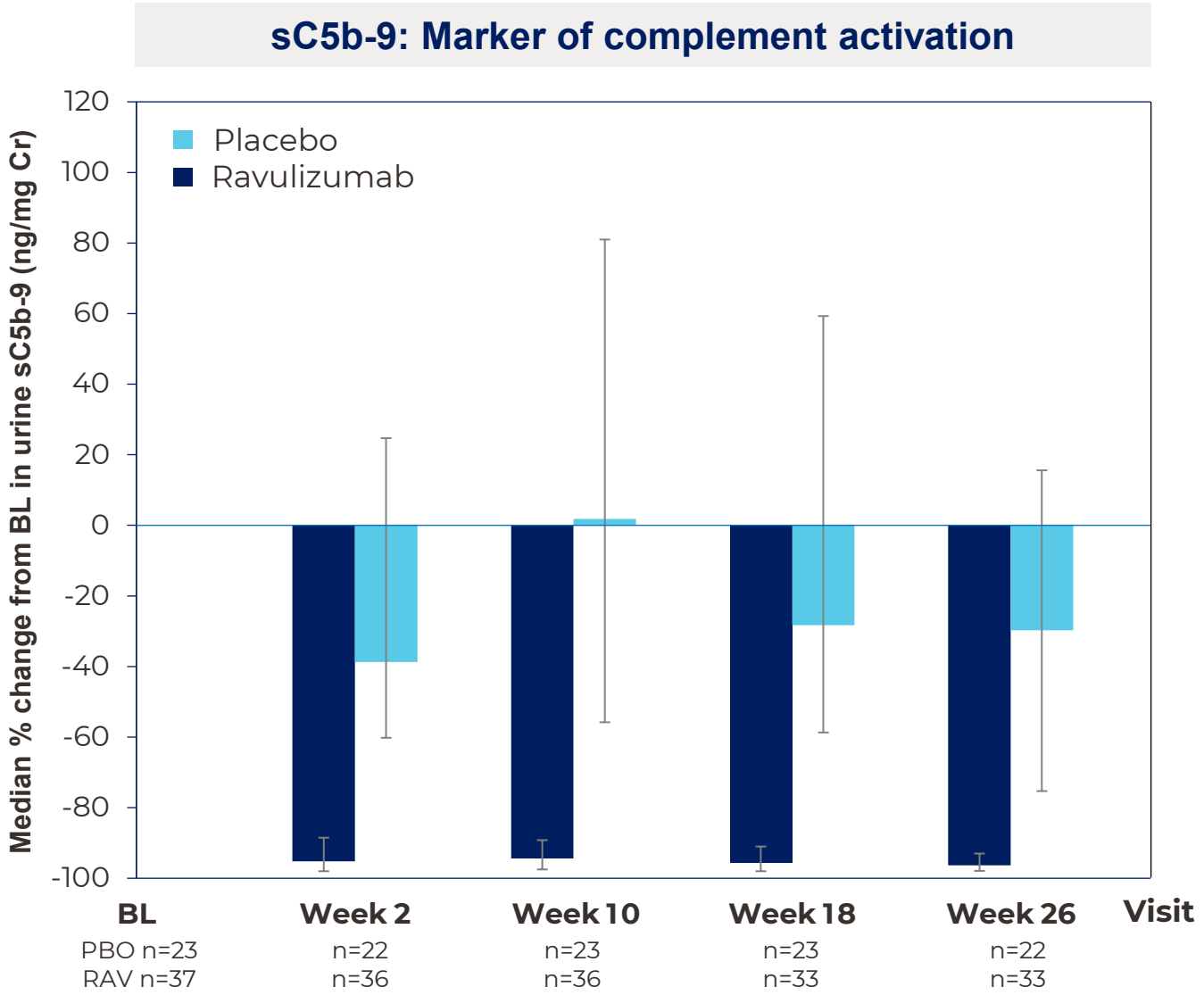
- Spot urine samples were collected pre-dose on Days 1, 15, 71, 127, and 183 (initial evaluation period); Day 351 (extension period)
- Urinary biomarker levels were normalized to matched urine creatinine

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

Results: Change in Urine sC5b-9/Cr Over Time

- **95.2%** median reduction by Week 2 (vs 38.7% for placebo)
- Consistent with reduction in proteinuria that was observed as early as Week 10[1]
- Effect sustained through Week 26

MMRM LS mean (95% CI) change from BL to Week 26*		
RAV	**PBO**	**p-value#**
-4.5 (-4.8, -4.1)	-0.7 (-1.2, -0.3)	**<0.0001**



*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.

#p-values shown are from the MMRM model.

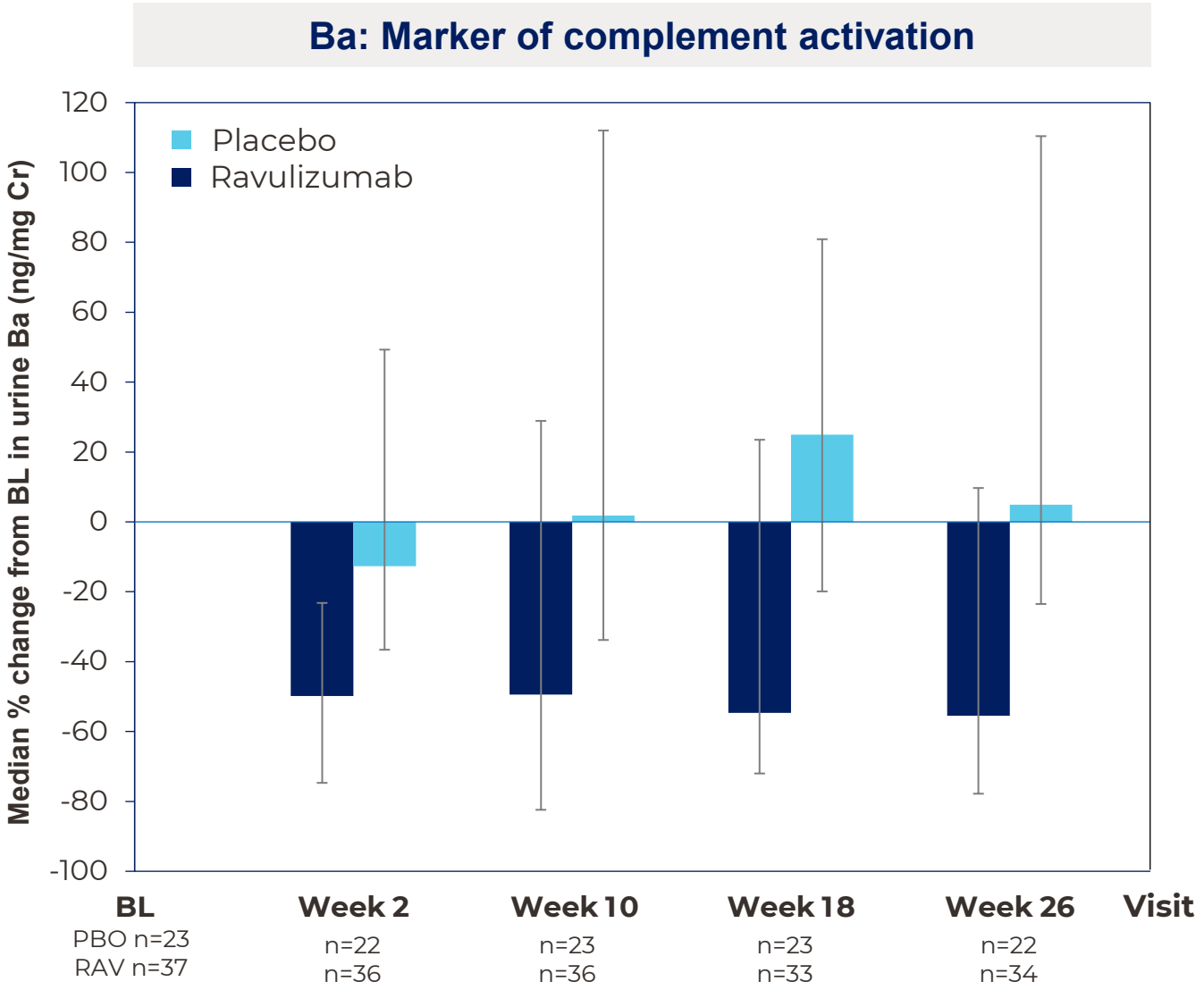
BL, baseline; CI, confidence interval; Cr, creatinine; LS, least squares; MMRM, mixed model for repeated measures; PBO, placebo; RAV, ravulizumab; sC5b-9, soluble membrane attack complex.

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

Results: Change in Urine Ba/Cr Over Time

- **49.8%** median reduction by Week 2 (vs 12.7% for placebo)
- Consistent with reduction in proteinuria that was observed as early as Week 10[1]
- Effect sustained through Week 26, suggesting C5 inhibition reduces complement activity in the kidney

MMRM LS mean (95% CI) change from BL to Week 26*		
RAV	**PBO**	**p-value#**
-1.1 (-1.6, -0.7)	0.4 (-0.3, 1.0)	**0.0003**



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Ba, complement factor Ba; BL, baseline; CI, confidence interval; Cr, creatinine; LS, least squares; MMRM, mixed model for repeated measures; PBO, placebo; RAV, ravulizumab.

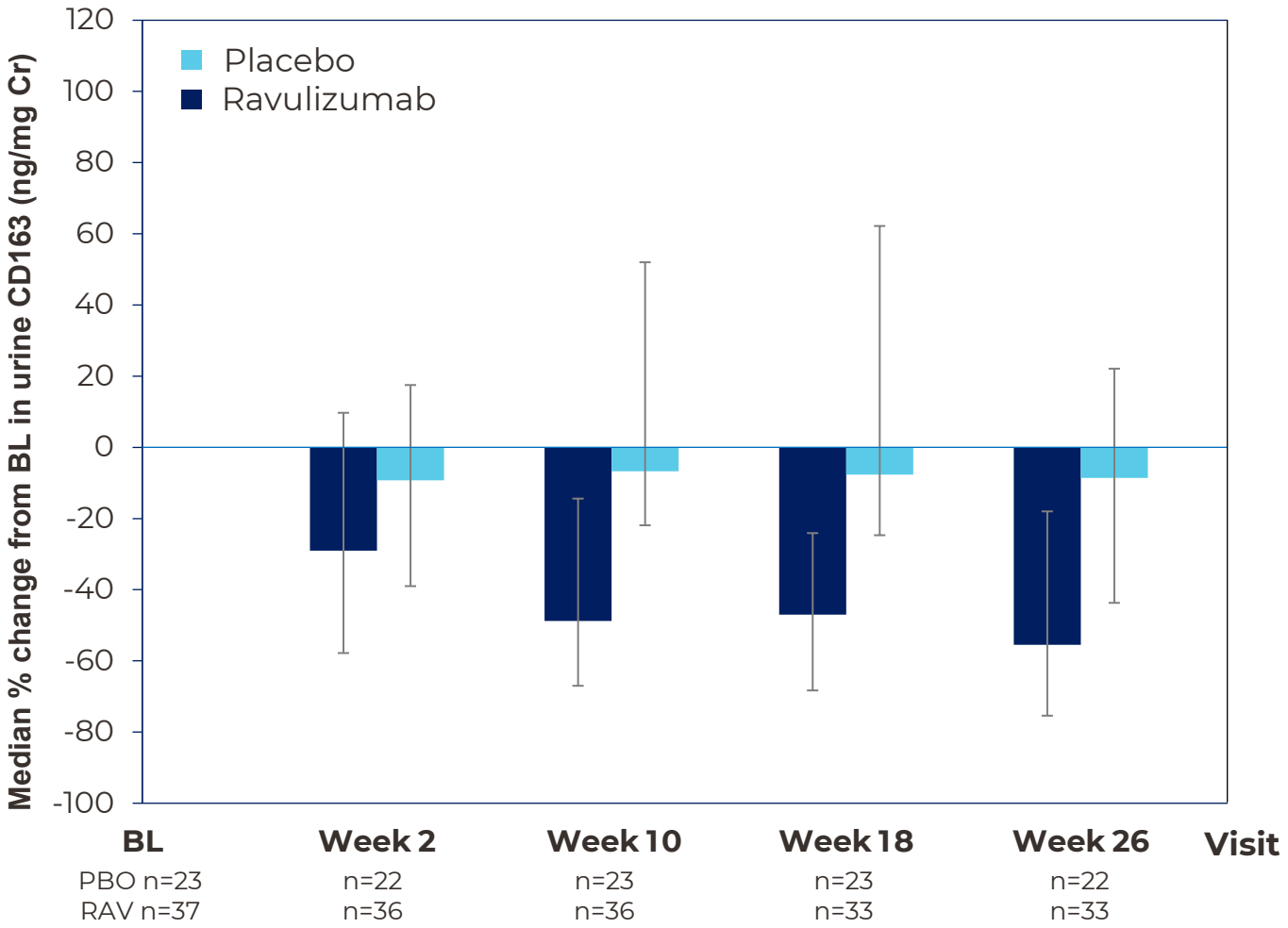
1. Lafayette R, et al. *J Am Soc Nephrol*. 2025;36(4):645–656.

Results: Change in Urine CD163/Cr Over Time

- **48.8%** median reduction observed by Week 10 (vs 6.7% for placebo)
- Effect sustained through Week 26

MMRM LS mean (95% CI) change from BL to Week 26*		
RAV	**PBO**	**p-value#**
-1.1 (-1.5, -0.7)	-0.2 (-0.7, 0.2)	**0.0036**

CD163: Marker of macrophage renal infiltration



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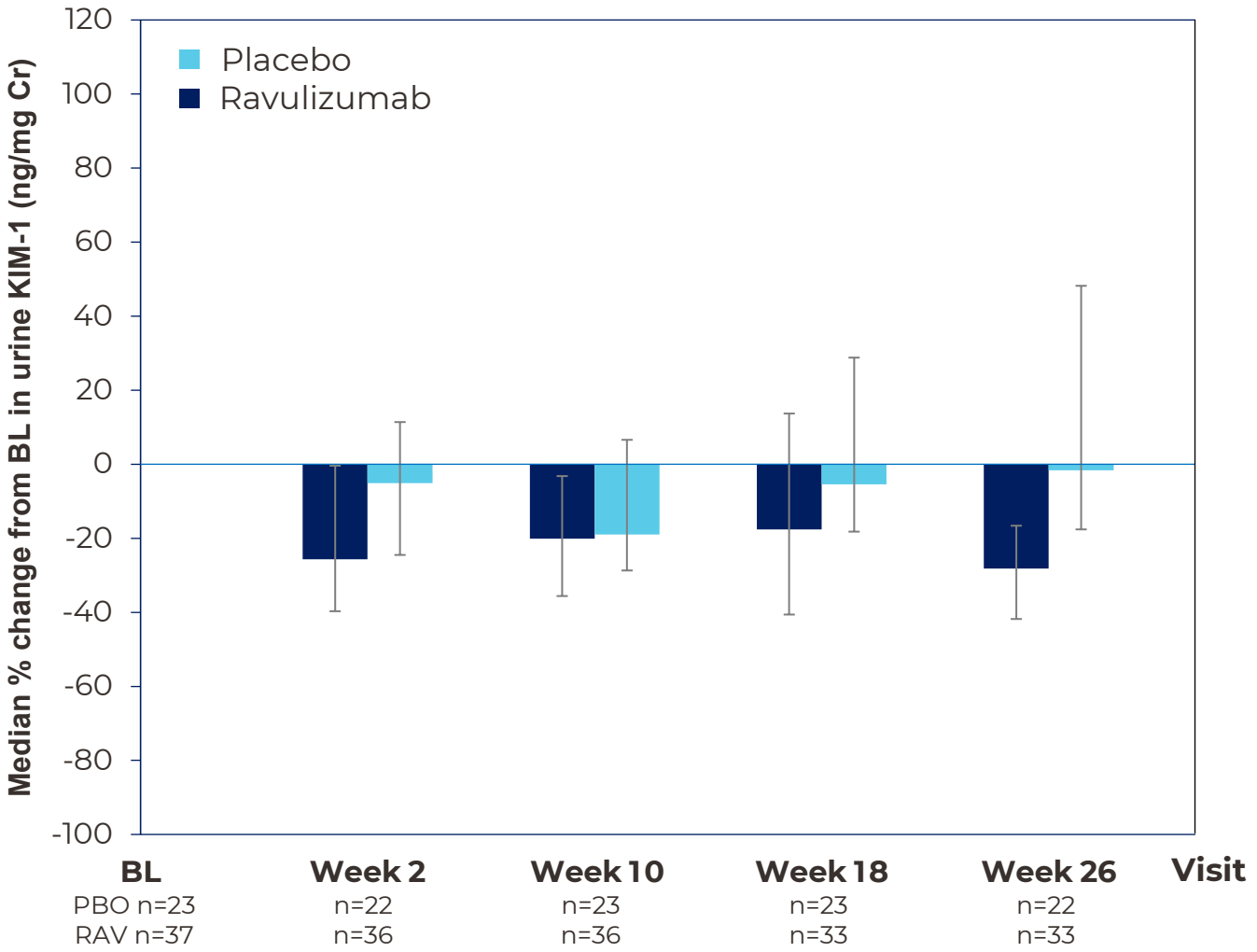
#p-values shown are from the MMRM model.
BL, baseline; CD163, cluster of differentiation 163; CI, confidence interval; Cr, creatinine; LS, least squares; MMRM, mixed model for repeated measures; PBO, placebo; RAV, ravulizumab.

Results: Change in Urine KIM-1/Cr Over Time

- **28.2%** median reduction observed by Week 26 (vs 1.6% for placebo)
- Significant difference in mean change from baseline to Week 26

MMRM LS mean (95% CI) change from BL to Week 26*		
RAV	**PBO**	**p-value#**
-0.6 (-0.8, -0.4)	0.1 (-0.2, 0.4)	**0.0001**

KIM-1: Specific marker of renal proximal tubule injury



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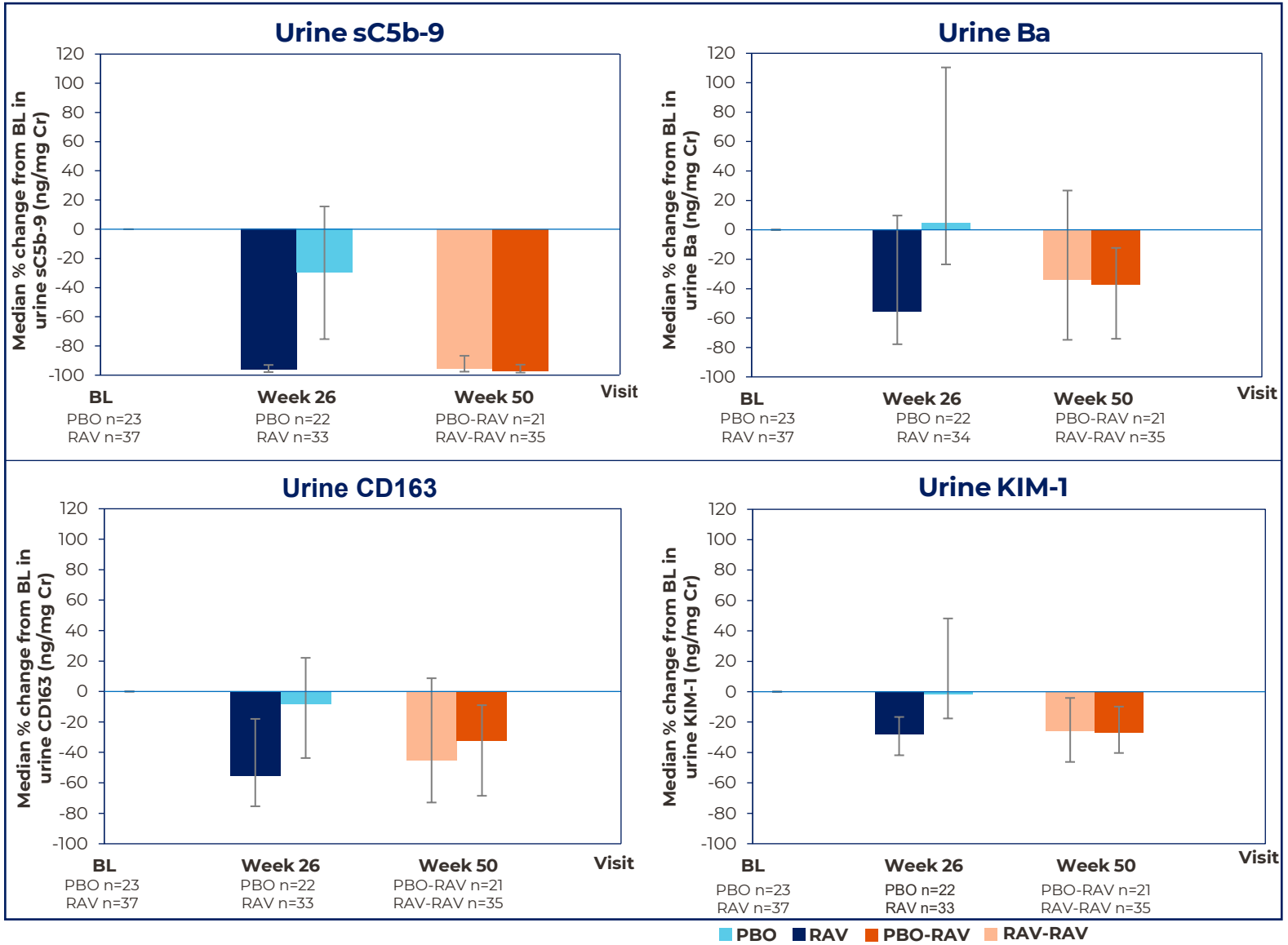
#p-values shown are from the MMRM model.
BL, baseline; CI, confidence interval; Cr, creatinine; KIM-1, kidney injury molecule-1; LS, least squares; MMRM, mixed model for repeated measures; PBO, placebo; RAV, ravulizumab.

Results: Change in Biomarkers During Extension Phase

- Effect sustained **through Week 50**
- Effect further validated in PBO-RAV group after Week 26 crossover

MMRM LS mean (95% CI) change from BL to Week 50*			
	RAV-RAV	**PBO-RAV**	**p-value**
Urine sC5b-9/Cr	-3.9 (-4.5, -3.4)	-4.5 (-5.2, -3.8)	ns
Urine Ba/Cr	-0.8 (-1.4, -0.3)	-1.1 (-1.8, -0.4)	ns
Urine CD163/Cr	-1.0 (-1.4, -0.5)	-0.9 (-1.5, -0.4)	ns
Urine KIM-1/Cr	-0.6 (-0.8, -0.3)	-0.5 (-0.9, -0.2)	ns



11 *LS mean change from baseline values are based on MMRM model.
Ba, complement factor Ba; BL, baseline; CI, confidence interval; CD163, cluster of differentiation 163; KIM-1, kidney injury molecule-1; LS, least squares; MMRM, mixed model for repeated measures; ns, not significant; PBO, placebo; RAV, ravulizumab; sC5b-9, soluble membrane attack complex.

Conclusions

- In patients treated with **ravulizumab**, there was an **early and sustained reduction** (including through **Weeks 26-50**) in urine complement activation markers **sC5b-9 and Ba**
- **Sustained reduction** (including through **Weeks 26-50**) was also observed in renal macrophage infiltration marker **CD163** and in proximal tubule injury marker **KIM-1** in patients treated with **ravulizumab**
- Reduction in biomarker levels observed in **RAV-RAV** group was also observed in **PBO-RAV** group, through **Weeks 26-50** after **crossover at Week 26**
- Our findings suggest **reduced inflammation** and **kidney damage** in response to **C5** (terminal complement) **inhibition** with **ravulizumab**
- This is consistent with the observed **proteinuria reduction** in the **SANCTUARY trial**[1] and provides insights into the pathophysiology of **IgA nephropathy**

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

Ba, complement factor Ba; CD163, cluster of differentiation 163; KIM-1, kidney injury molecule-1; PBO, placebo; RAV, ravulizumab; sc5b-9, soluble membrane attack complex.

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