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Enclosure:

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Sibeprenlimab in IgA Nephropathy: Achievement of Target Proteinuria Thresholds in the Phase 3 VISIONARY Trial Interim Post Hoc Analysis

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SPRING CLINICAL MEETINGS

Disclosures

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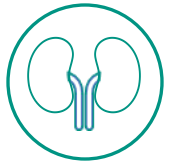
Learning Objectives

1. To evaluate the treatment response of sibeprenlimab across different proteinuria thresholds, in alignment with KDIGO-recommended targets that recognize proteinuria reduction as a key marker of improved kidney outcomes
2. To use response rates of proteinuria targets to calculate the numbers needed to treat (NNT), which helps determine the clinical benefit of treatment with sibeprenlimab

IgA nephropathy is a progressive, immune-mediated chronic kidney disease

IgA nephropathy is the **most common glomerulonephritis worldwide**[1,2]

IgA nephropathy is most often diagnosed in adults between **20 and 40 years of age**[3]



A substantial proportion of patients with IgA nephropathy, even those classified as low risk,[a] **progress to end-stage kidney disease within 10-15 years of diagnosis**[4]

The KDIGO 2025 guideline for IgA nephropathy emphasizes **proteinuria reduction as a treatment goal,** with lower proteinuria thresholds associated with improved renal outcomes. Sustained proteinuria <0.5 g/d, and ideally <0.3 g/d, is a key treatment target[5]

[a]Proteinuria <1 g/d.

IgA, immunoglobulin A; KDIGO, Kidney Disease: Improving Global Outcomes.

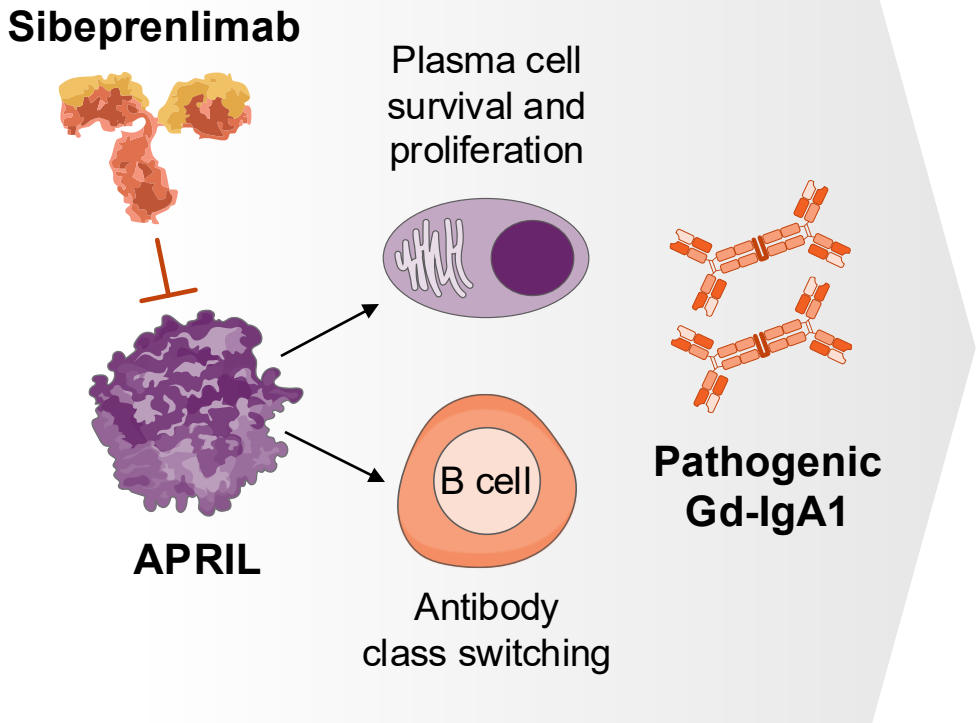
1. Cheung CK, et al. *Nat Rev Nephrol*. 2025;21(1):9-23. **2.** McGrogan A, et al. *Nephrol Dial Transplant*. 2011;26(2):414-430. **3.** Perkovic V, et al. *N Engl J Med*. 2026;394(7):635-646. **4.** Pitcher D, et al. *Clin J Am Soc Nephrol*. 2023;18(6):727-738. **5.** KDIGO. *Kidney Int*. 2025;108(4S):S1-S71.

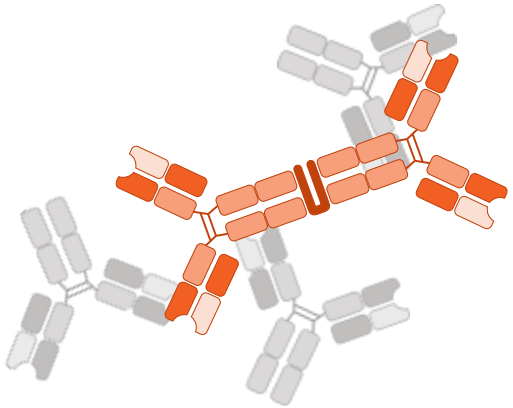
Sibeprenlimab selectively blocks APRIL, a key driver of IgA nephropathy pathogenesis

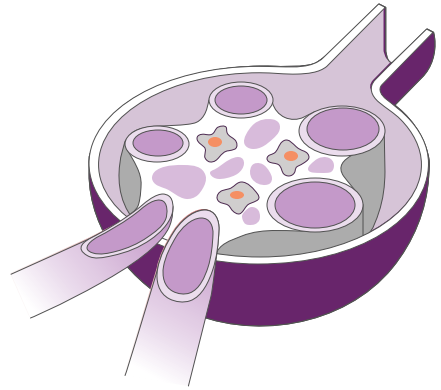
Sibeprenlimab is a humanized IgG2 mAb that selectively blocks APRIL, reducing pathogenic Gd-IgA1

Gd-IgA1–autoantibody immune complex formation

Immune complex deposition in glomeruli







Leading to kidney damage and loss of function

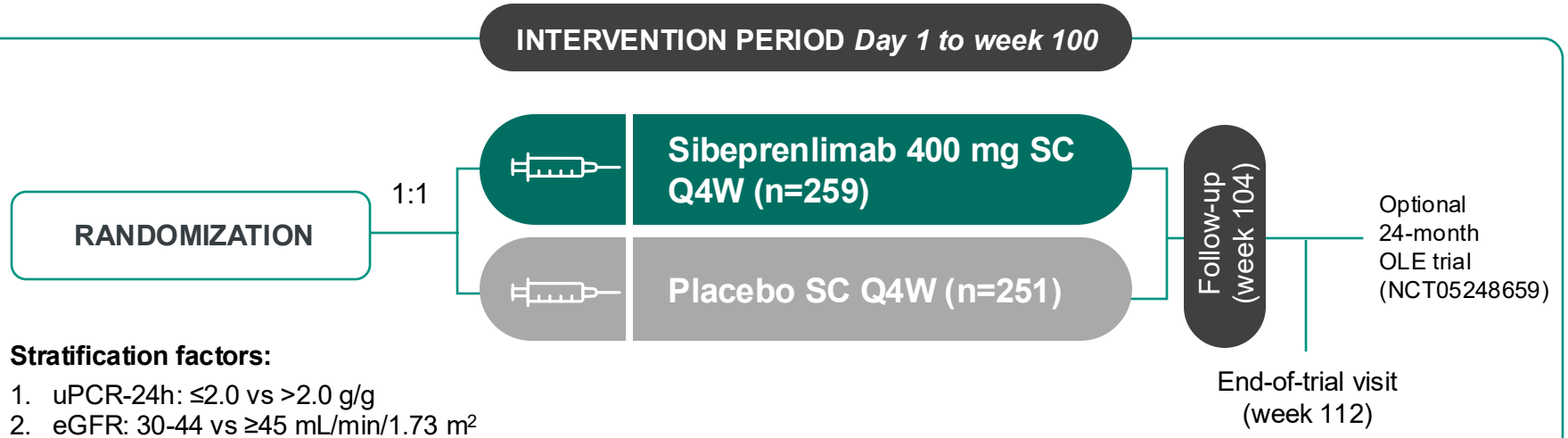
APRIL, a proliferation-inducing ligand; Gd-IgA1, galactose-deficient immunoglobulin A1; IgA, immunoglobulin A; IgG2, immunoglobulin G2; mAb, monoclonal antibody.

Perkovic V, et al. *N Engl J Med*. 2026;394(7):635-646.

VISIONARY Phase 3: Trial design

Key inclusion criteria

- Biopsy-confirmed IgA nephropathy
- Age ≥18 years
- uPCR ≥0.75 g/g or urine protein ≥1.0 g/d
- eGFR ≥30 mL/min/1.73 m^2
- Stable or maximally tolerated dose of ACEi and/or ARB with or without SGLT2i for ≥3 months



Stratification factors:

1. uPCR-24h: ≤2.0 vs >2.0 g/g
2. eGFR: 30-44 vs ≥45 mL/min/1.73 m^2
3. SGLT2i use: Yes or no

Primary endpoint

- uPCR at 9 months vs baseline based on 24-hour urine collection

Secondary endpoints

- Key: Annualized slope of eGFR estimated over ~24 months
- Other: Safety; change from baseline in total serum IgA, IgG, and IgM

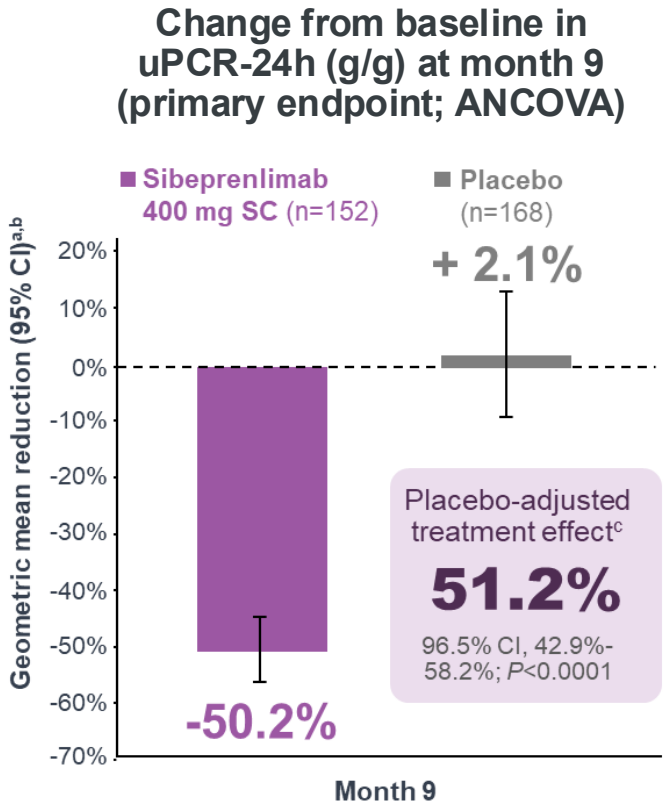
Exploratory endpoints

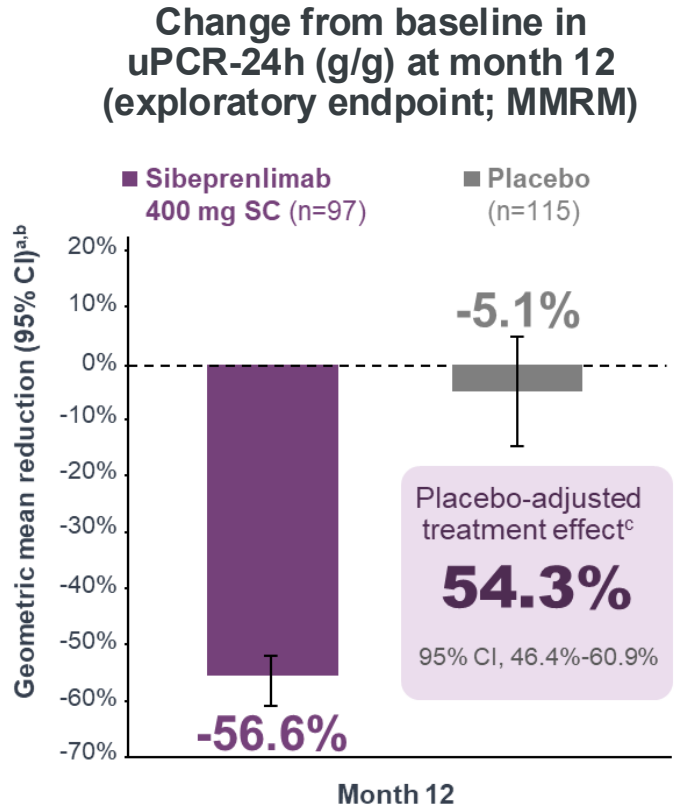
- Change from baseline in uPCR-24h at 12 months
- Change in spot uPCR, hematuria, serum Gd-IgA1, and APRIL concentrations and proteinuric remission (urine total protein <0.5 g/d at 12 months)

ACEi, angiotensin-converting enzyme inhibitor; APRIL, a proliferation-inducing ligand; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; Gd-IgA1, galactose-deficient immunoglobulin A1; Ig, immunoglobulin; OLE, open-label extension; Q4W, every 4 weeks; SC, subcutaneous; SGLT2i, sodium-glucose cotransporter 2 inhibitor; uPCR, urine protein to creatinine ratio; uPCR-24h, urine protein to creatinine ratio based on 24-hour urine collections.

Sibeprenlimab resulted in significant reduction in proteinuria compared with placebo

- In the interim analysis (N=320), 62.5% of study participants were men, 59.1% were Asian, mean age was 42.8 years, and mean uPCR-24h was 1.54 g/g
- Sibeprenlimab was well tolerated in patients with IgA nephropathy
- Sibeprenlimab was granted accelerated approval for the reduction of proteinuria in adults with primary IgA nephropathy at risk for disease progression by the US Food and Drug Administration on November 25, 2025[1]





Previously presented at the American Society of Nephrology Annual Meeting, November 5-9, 2025, Houston, TX, USA and at UK Kidney Week, March 10-12, 2026, Harrogate, UK.
[a]The interim analysis set comprises the first 62.5% of randomized participants who had the opportunity to complete the 9-month (week 40) 24-hour uPCR evaluation. [b]The percentage reduction of uPCR-24h at month 9 is compared to baseline using ANCOVA, calculated as (1 – GM of uPCR-24h ratio estimated from ANCOVA model) x 100%. [c]The percentage reduction for treatment effect was calculated as (1 – ratio of GM of uPCR-24h ratio for sibeprenlimab 400 mg SC over placebo estimated from ANCOVA model) x 100%. The 95% CI corresponds to the treatment-specific reductions, while the 96.5% CI corresponds to the between-treatment difference, aligned with the predefined split alpha of 0.035 used for testing the 24-hour uPCR endpoint in the interim analysis.
ANCOVA, analysis of covariance; CI, confidence interval; GM, geometric mean; IgA, immunoglobulin A; MMRM, mixed model for repeated measures; SC, subcutaneous; uPCR-24h, urine protein to creatinine ratio based on 24-hour urine collections.
1. VOYXACT (sibeprenlimab-szsi) [prescribing information]. Tokyo, Japan: Otsuka America Pharmaceutical Company, Ltd; November 2025.

VISIONARY PHASE 3: Post hoc analysis of proteinuria targets

Key inclusion criteria

- Biopsy-confirmed IgA nephropathy
- Age ≥18 years
- uPCR ≥0.75 g/g or urine protein ≥1.0 g/d
- eGFR ≥30 mL/min/1.73 m^2
- Stable or maximally tolerated dose of ACEi and/or ARB with or without SGLT2i for ≥3 months

Primary endpoint

- uPCR at 9 months vs baseline based on 24-hour urine collection

Secondary endpoints

- Key: Annualized slope of eGFR estimated over ~24 months
- Other: Safety; change from baseline in total serum IgA, IgG, and IgM

Exploratory endpoints

- Change from baseline in uPCR-24h at 12 months
- Change in spot uPCR, hematuria, serum Gd-IgA1, and APRIL concentrations and proteinuric remission (urine total protein <0.5 g/d at 12 months)

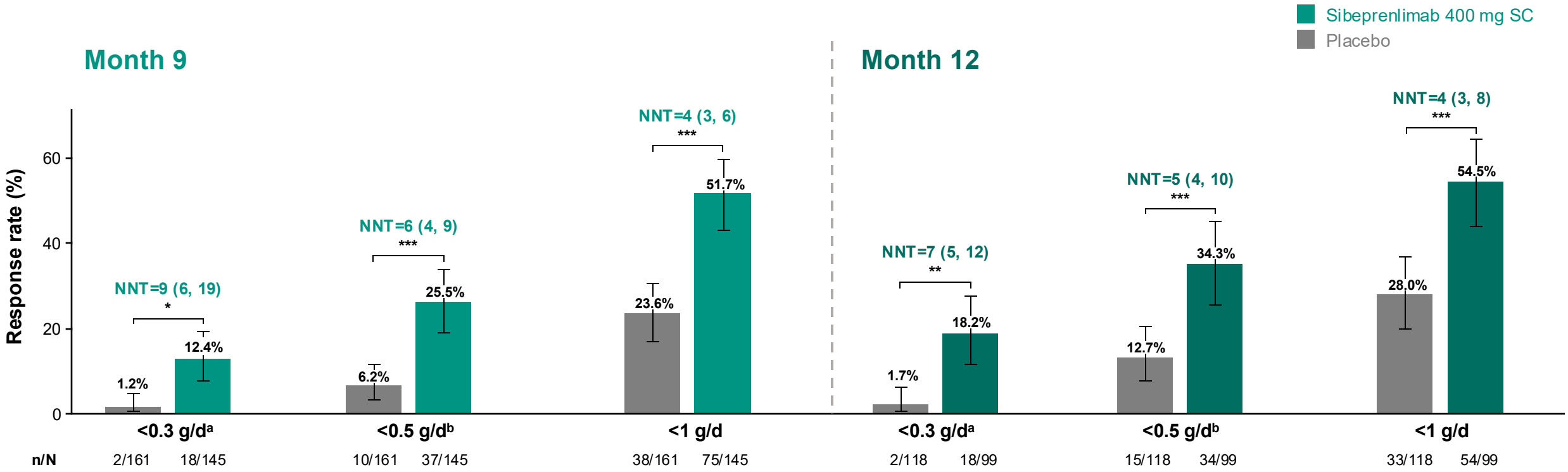
Post hoc analysis[a]

- **Evaluation of categorical proteinuria response rates using observed Phase 3 IA data at 9 and 12 months**
  - Urine total protein, uPCR-24h reduction, protein excretion reduction
- **Numbers needed to treat (NNT) were calculated to determine how many patients would require treatment with sibeprenlimab instead of placebo for 1 additional patient to achieve each proteinuria target**

[a]For proteinuria targets, urine total protein threshold of <0.3 g/d was calculated post hoc, while <0.5 g/d and <1 g/d were prespecified; achievement of ≥30%, ≥40%, and ≥50% reductions in uPCR-24h from baseline and achievement of ≥30%, ≥40%, and ≥50% protein excretion were calculated post hoc.

ACEi, angiotensin-converting enzyme inhibitor; APRIL, a proliferation-inducing ligand; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; Gd-IgA1, galactose-deficient immunoglobulin A1; IA, interim analysis; Ig, immunoglobulin; OLE, open-label extension; Q4W, every 4 weeks; SC, subcutaneous; SGLT2i, sodium-glucose cotransporter 2 inhibitor; uPCR, urine protein to creatinine ratio; uPCR-24h, urine protein to creatinine ratio based on 24-hour urine collections.

Sibeprenlimab produced significantly higher response rates than placebo in achieving proteinuria <0.3, <0.5, and <1 g/d

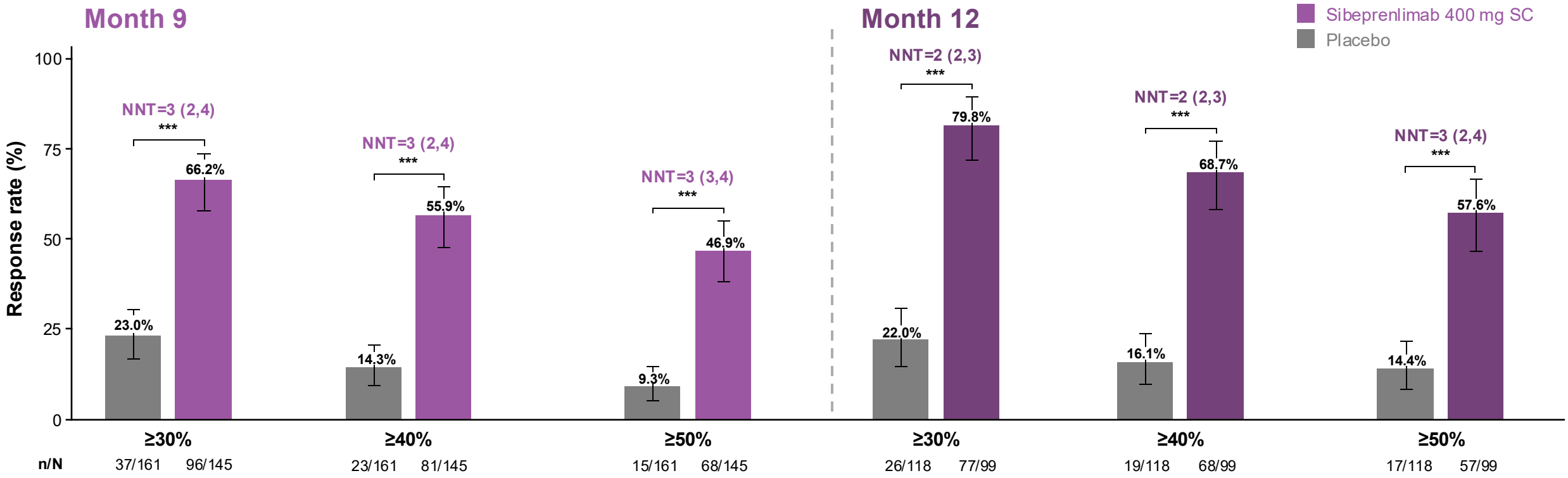


For every **9, 6, and 4 patients** treated with sibeprenlimab instead of placebo, **1 additional treatment response** would be achieved at <0.3, <0.5, and <1 g/d thresholds, respectively

For every **7, 5, and 4 patients** treated with sibeprenlimab instead of placebo, **1 additional treatment response** would be achieved at <0.3, <0.5, and <1 g/d thresholds, respectively

*P<0.05, **P<0.001, ***P<0.0001.
The percentages of patients achieving <0.5 g/d or <1 g/d urine total protein reduction were prespecified analyses, whereas <0.3 g/d urine total protein reduction and the NNT values were post hoc analyses.
[a]Ideal treatment goal per 2025 KDIGO guidelines for IgA nephropathy. [b]Recommended treatment goal per 2025 KDIGO guidelines for IgA nephropathy.
IgA, immunoglobulin A; KDIGO, Kidney Disease: Improving Global Outcomes; NNT, number needed to treat; SC, subcutaneous.

Sibeprenlimab produced significantly higher response rates vs placebo in achieving ≥30%, ≥40%, and ≥50% reduction in uPCR-24h



For every **3 patients** treated with sibeprenlimab instead of placebo, **1 additional treatment response** would be achieved at each threshold

1 additional treatment response would be achieved for every **2 patients** treated with sibeprenlimab vs placebo at the ≥30% and ≥40% thresholds and for every **3 patients** at the ≥50% threshold

- Similar results were observed for ≥30%, ≥40%, and ≥50% protein excretion

***P<0.0001.
The percentages of patients achieving ≥30%-50% uPCR-24h reduction and NNT values were post hoc analyses.
NNT, number needed to treat; SC, subcutaneous; uPCR-24h, urine protein to creatinine ratio based on 24-hour urine collections.

Conclusions

In a post hoc analysis of the phase 3 VISIONARY trial interim analysis, sibeprenlimab led to significantly higher response rates across all categorical proteinuria targets at 9 months that were maintained at 12 months

- Proteinuria targets included proteinuria <0.3, <0.5, and <1 g/d; ≥30%, ≥40%, and ≥50% reduction in uPCR-24h; and ≥30%, ≥40%, and ≥50% reduction in 24-hour protein excretion

NNT values ranged from 2 to 9 across proteinuria targets and generally trended downward over time

Nearly one-third of patients receiving sibeprenlimab achieved urine protein <0.5 g/d at month 12, aligning with evolving KDIGO treatment goals and providing clinically meaningful measures to support treatment decision-making in IgA nephropathy

The low NNT values and consistent benefit across all proteinuria thresholds reinforce the clinically meaningful efficacy of sibeprenlimab in IgA nephropathy

VISIONARY is ongoing and will continue to evaluate the safety and efficacy of sibeprenlimab, including effects on eGFR, over a 24-month treatment period

eGFR, estimated glomerular filtration rate; IgA, immunoglobulin A; KDIGO, Kidney Disease: Improving Global Outcomes; NNT, number needed to treat; uPCR-24h, urine protein to creatinine ratio based on 24-hour urine collections.

Questions?

Pre-Test Question

Q: An NNT analysis provides information about the potential clinical benefit of a treatment. (T/F)

A: True

R: NNT analysis tells us how many patients would require treatment with active drug instead of placebo for 1 additional patient to achieve a specified treatment goal.

Post-Test Question

Q: The NNT analysis demonstrated a clinical benefit of sibeprenlimab versus placebo in patients with IgA nephropathy. (T/F)

A: True

R: NNT values for sibeprenlimab versus placebo were descriptively lower at less stringent response thresholds and at 12 months versus 9 months, demonstrating that fewer patients required treatment with active drug instead of placebo for 1 additional patient to achieve the specified proteinuria targets.