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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

G-487

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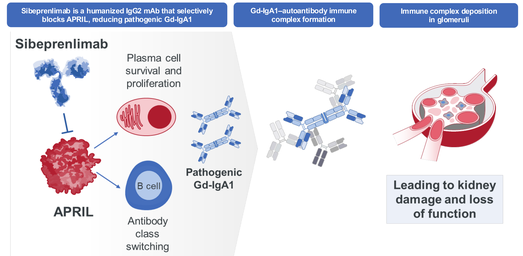
## INTRODUCTION

- Immunoglobulin A (IgA) nephropathy, a progressive immune-mediated chronic kidney disease, represents the most common form of primary glomerulonephritis worldwide and is most often diagnosed in adults between 20 and 40 years of age[1-3]
  - A substantial proportion of patients with IgA nephropathy, even those previously classified as low risk (ie, proteinuria <1 g/d), progress to end-stage kidney disease within 10-15 years of diagnosis[4]
- The Kidney Disease: Improving Global Outcomes (KDIGO) 2025 Clinical Practice Guideline for the Management of IgA Nephropathy highlights proteinuria as the only currently available validated short-term, modifiable biomarker that informs the future risk of kidney function decline[5]
- Sibeprenlimab is a humanized immunoglobulin G2 (IgG2) monoclonal antibody that selectively blocks a proliferation-inducing ligand (APRIL), a key driver of IgA nephropathy pathogenesis (**Figure 1**).[2,6] APRIL selectively modulates B-cell functions that support the production of pathogenic galactose-deficient immunoglobulin A1 (Gd-IgA1) and immune complex deposition, leading to kidney damage and loss of function[7-9]

**Figure 1. Sibeprenlimab mechanism of action**[2,6,9]




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

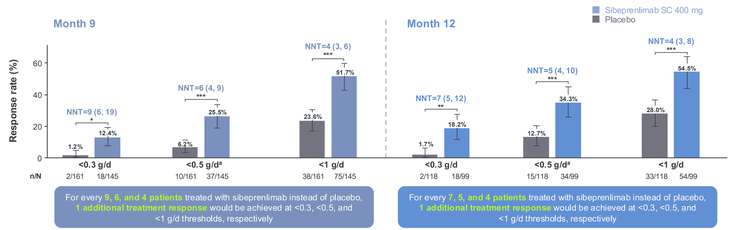
- In a prespecified interim analysis of the global VISIONARY trial (NCT05248646), demographic and clinical characteristics were balanced across sibeprenlimab and placebo arms, including age, sex, baseline kidney function, and background therapy use[2]
  - Baseline proteinuria levels were comparable between treatment arms, with mean (SD) 24-hour urine protein to creatinine ratio (uPCR-24h) of 1.58 (1.09) vs 1.50 (0.84) g/g and mean (SD) urine protein of 2.19 (1.47) vs 2.04 (1.22) g/d in the sibeprenlimab and placebo groups, respectively
- Sibeprenlimab achieved a 51.2% (*P*<0.001) placebo-adjusted reduction in uPCR-24h at the 9-month interim analysis and was well tolerated in patients with IgA nephropathy[2,10]
  - Sibeprenlimab also led to a 54.3% (95% confidence interval [CI], 46.4-60.9) placebo-adjusted reduction in uPCR-24h at 12 months[2]
- 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[11]
- The 2025 KDIGO guideline for IgA nephropathy emphasizes proteinuria reduction as a treatment goal, with lower proteinuria thresholds associated with improved renal outcomes[5]
  - The KDIGO 2025 guideline highlights sustained proteinuria <0.5 g/d as a key treatment target, with lower levels (<0.3 g/d) associated with further reduction in progression risk[5]
- Evaluating clinically relevant proteinuria thresholds helps translate trial results into measures that are more meaningful for clinicians; number needed to treat (NNT) further illustrates treatment impact by showing how many patients must be treated for one patient to achieve a target proteinuria response, with lower values indicating greater treatment benefit[12]
- Here, we report on post hoc analysis evaluating 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

## RESULTS

- For proteinuria targets of <0.3, <0.5, and <1 g/d, patients treated with sibeprenlimab achieved significantly higher response rates vs placebo at months 9 and 12, with NNT values decreasing from month 9 to month 12 (**Figure 2A**)
  - At month 9, 25% of patients receiving sibeprenlimab achieved <0.5 g/d vs 6.2% of patients on placebo, with 1 additional patient achieving this target for every 6 patients treated with sibeprenlimab (NNT=6); the NNT decreased to 5 at month 12
- For ≥30%, ≥40%, and ≥50% reductions in uPCR-24h, patients treated with sibeprenlimab achieved significantly higher response rates vs placebo at months 9 and 12, with NNT values decreasing from month 9 to month 12 (and maintained for the ≥50% threshold) (**Figure 2B**)
  - Approximately 50% of patients receiving sibeprenlimab achieved ≥50% reduction in uPCR-24h at month 9 vs <10% with placebo; response rates increased by ~10% at month 12 with sibeprenlimab, with NNT remaining 3 at both time points

**Figure 2. Response analysis of different proteinuria targets**

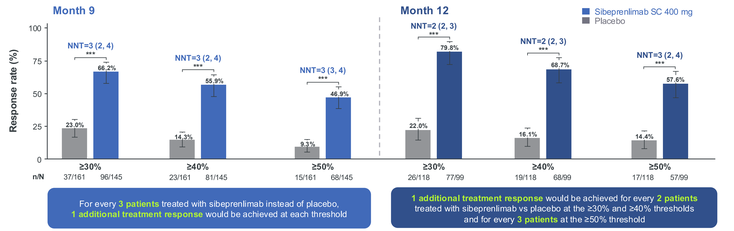
A) Response analysis of patients achieving <0.3, <0.5, or <1 g/d urine total protein-24h at months 9 and 12




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

B) Response analysis of patients achieving ≥30%, ≥40%, or ≥50% reduction in uPCR-24h at months 9 and 12




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

*P<0.05, **P<0.001, ***P<0.0001.
The percentages of patients achieving ≥30%-50% uPCR reduction and <0.3 g/d urine total protein and the NNT values are post hoc analyses.
The percentages of patients achieving <0.5 g/d or <1 g/d urine total protein are prespecified analyses.
[a]Recommended treatment goal per 2025 KDIGO guideline for IgA nephropathy.
IgA, immunoglobulin A; KDIGO, Kidney Disease: Improving Global Outcomes; NNT, number needed to treat; SC, subcutaneous; uPCR, urine protein to creatinine ratio; uPCR-24h, urine protein to creatinine ratio based on 24-hour urine collection; urine total protein-24h, urine total protein based on 24-hour urine collection.

## CONCLUSIONS

- In 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, which were maintained at 12 months. NNT values ranged from 2-9 across proteinuria targets and generally trended downward over time
- Approximately 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 estimated glomerular filtration rate, over a 24-month treatment period

- Response rates for reductions in 24-h protein excretion were also significantly higher with sibeprenlimab vs placebo. At month 9, 69.7% of patients receiving sibeprenlimab achieved ≥30% reduction vs 26.1% with placebo (NNT [95% CI]=3 [2, 3]); this increased to 76.8% vs 29.7%, respectively, at month 12 (NNT [95% CI]=3 [2, 3])
  - Response rates for ≥40% and ≥50% reductions were also higher with sibeprenlimab vs placebo at both 9 and 12 months
- Summary of key response rates at months 9 and 12 for <0.5 g/d urine protein and ≥50% reduction in uPCR-24h proteinuric targets is given in **Table 1**

**Table 1. Summary of key response rates and associated NNT values at months 9 and 12**

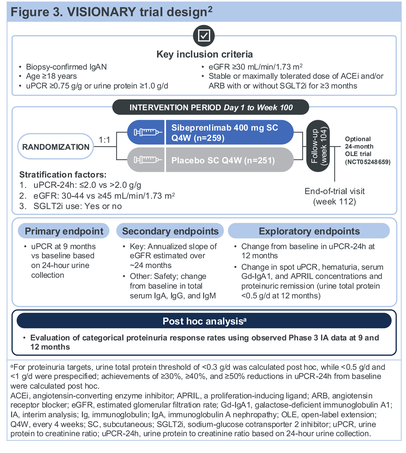
| Proteinuria target[a] | Sibeprenlimab 400 mg SC, n (%) (9 mo: N=145) (12 mo: N=99) | Placebo, n (%) (9 mo: N=161) (12 mo: N=118) | Sibeprenlimab vs placebo NNT[b] (95% CI) |
|---|---|---|---|
| **Urine total protein-24h <0.5 g/d[c]** | | | |
| Month 9 | 37 (25.5%) | 10 (6.2%) | **6 (4, 9)** |
| Month 12 | 34 (34.3%) | 15 (12.7%) | **5 (4, 10)** |
| **≥50% reduction from baseline in uPCR-24h** | | | |
| Month 9 | 68 (46.9%) | 15 (9.3%) | **3 (3, 4)** |
| Month 12 | 57 (57.6%) | 17 (14.4%) | **3 (2, 4)** |

[a]The percentages of patients achieving <0.5 g/d urine total protein are prespecified analyses. The percentages of patients achieving ≥50% uPCR reduction and the NNT values are post hoc analyses.
[b]NNT = x: For every x patients treated with sibeprenlimab instead of placebo, 1 additional treatment response would be achieved.
[c]Recommended treatment goal per 2025 KDIGO guidelines for IgA nephropathy.
CI, confidence interval; IgA, immunoglobulin A; KDIGO, Kidney Disease: Improving Global Outcomes; mo, months; NNT, number needed to treat; SC, subcutaneous; uPCR-24h, urine protein to creatinine ratio based on 24-hour urine collection; urine total protein-24h, urine total protein based on 24-hour urine collection.

## METHODS

- VISIONARY is a Phase 3, randomized, multicenter, double-blind, placebo-controlled trial in adults with biopsy-confirmed IgA nephropathy. Eligible patients were randomized 1:1 to sibeprenlimab or placebo every 4 weeks for 100 weeks (**Figure 3**)[2]

**Figure 3. VISIONARY trial design**[2]




[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; achievements of ≥30%, ≥40%, and ≥50% reductions in uPCR-24h from baseline 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; IgA, immunoglobulin A nephropathy; 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 collection.

- Patients randomized to subcutaneous sibeprenlimab 400 mg or placebo were evaluated for categorical proteinuria responses using observed data at 9 and 12 months. This analysis included 306 patients at month 9 and 217 at month 12 (interim analysis population: N=320; sibeprenlimab: n=152; placebo: n=168; data cutoff: September 4, 2024)
- Response rates were assessed across various proteinuria thresholds, including
  - The percentages of patients achieving a urine total protein of <0.3 g/d (post hoc analyses), <0.5 g/d, or <1 g/d (prespecified analyses)
  - The percentages of patients achieving ≥30%, ≥40%, or ≥50% uPCR-24h reductions from baseline (post hoc analyses)
- In post hoc analysis, NNTs were calculated to determine how many patients would require treatment with sibeprenlimab instead of placebo for 1 additional patient to achieve each proteinuria target
  - NNT is calculated as 1 divided by the difference in response rates between sibeprenlimab and placebo

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DISCLOSURES

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SCAN TO VIEW