ORIGINAL ARTICLE

# Sibeprenlimab in IgA Nephropathy — Interim Analysis of a Phase 3 Trial

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## ABSTRACT

### BACKGROUND

The cytokine A proliferation-inducing ligand (APRIL) is considered a key driver of the pathogenesis of IgA nephropathy. Sibeprenlimab, a humanized IgG2 monoclonal antibody, selectively binds to and inhibits APRIL.

### METHODS

In this phase 3, multicenter, double-blind, randomized, placebo-controlled trial, we assigned adults with biopsy-confirmed IgA nephropathy in a 1:1 ratio to receive either subcutaneous sibeprenlimab at a dose of 400 mg or placebo administered every 4 weeks for 100 weeks. The primary end point for this interim analysis was the 24-hour urinary protein-to-creatinine ratio at 9 months as compared with baseline. The key secondary end point, to be reported at trial completion, is the annualized slope of estimated glomerular filtration rate over 24 months. Other secondary end points included the change in the level of serum immunoglobulin and safety. Exploratory end points included the change in galactose-deficient IgA1 and APRIL concentrations, the spot 24-hour urinary protein-to-creatinine ratio, hematuria, and remission of proteinuria.

### RESULTS

A total of 510 patients underwent randomization — 259 to the sibeprenlimab group and 251 to the placebo group. The prespecified interim analysis included the first 320 patients (152 who received sibeprenlimab and 168 who received placebo) who had the opportunity to complete the 9-month evaluation of the 24-hour urinary protein-to-creatinine ratio. At 9 months, a significant reduction in 24-hour urinary protein-to-creatinine ratio was observed with sibeprenlimab (–50.2%) as compared with an increase with placebo (2.1%), corresponding to an adjusted geometric least-squares mean 24-hour urinary protein-to-creatinine ratio that was 51.2% (96.5% confidence interval [CI], 42.9 to 58.2) lower with sibeprenlimab than with placebo ($P<0.001$). The levels of APRIL and pathogenic galactose-deficient IgA1 at week 48 were reduced from baseline by 95.8% and 67.1%, respectively, with sibeprenlimab. The safety profile appeared to be similar with sibeprenlimab and placebo. No deaths were reported, and the incidence of serious adverse events that occurred during the treatment period was 3.5% with sibeprenlimab and 4.4% with placebo.

### CONCLUSIONS

Sibeprenlimab resulted in a significant reduction in proteinuria as compared with placebo in patients with IgA nephropathy. (Funded by Otsuka Pharmaceutical Development and Commercialization. VISIONARY ClinicalTrials.gov number, NCT05248646.)

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IgA nephropathy is a progressive, immune-mediated kidney disease that is typically diagnosed in patients 20 to 40 years of age.[1,2] It is a leading cause of chronic kidney disease and the most common primary glomerulonephritis.[3,4] Despite supportive therapy, including blood-pressure control and use of renin–angiotensin system inhibitors or sodium–glucose cotransporter 2 inhibitors, many patients remain at risk for progression to kidney failure within 10 to 15 years after diagnosis.[5-8]

Mechanistic data have shown that IgA nephropathy is initiated by elevated levels of galactose-deficient IgA1, which trigger autoantibody formation and development of circulating immune complexes that deposit in the glomerular mesangium and which lead to hematuria, proteinuria, and kidney damage.[9] Proteinuria is an early marker of kidney injury and a strong predictor of long-term decline in kidney function. Reduction in proteinuria is consistently associated with preservation of kidney function, supporting its use as a surrogate end point for assessing treatment efficacy.[10,11]

Sibeprenlimab is a humanized IgG2 monoclonal antibody that selectively inhibits the cytokine A proliferation-inducing ligand (APRIL) by preventing it from binding to its receptors.[12,13] APRIL, considered to be a key driver of the pathogenesis of IgA nephropathy, mediates antibody class switching in mature B cells and plasma-cell survival, leading to the production of IgA and pathogenic galactose-deficient IgA1.[4,14]

In the phase 2 ENVISION trial, intravenous sibeprenlimab administered every 4 weeks for 12 months reduced proteinuria, stabilized the estimated glomerular filtration rate (eGFR), suppressed serum levels of APRIL, and decreased levels of galactose-deficient IgA1,[15] with an acceptable safety profile. The VISIONARY trial is an ongoing phase 3 trial evaluating the efficacy and safety of subcutaneous sibeprenlimab at a dose of 400 mg administered every 4 weeks in combination with supportive care in order to assess its ability to preserve kidney function in patients with IgA nephropathy.[16] Dose selection was based on the clinical effects of intravenous sibeprenlimab at a dose of 4 mg per kilogram of body weight shown in the phase 2 trial as well as modeling that showed that subcutaneous sibeprenlimab at a dose of 400 mg resulted in levels of exposure and IgA reduction that were similar to those with intravenous administration.[15,17] Here, we report the prespecified interim analysis of this phase 3 trial.

## Methods

### Trial Design and Oversight

This multicenter, double-blind, randomized, placebo-controlled phase 3 trial is being conducted at 240 sites across 31 countries. It is sponsored by Otsuka Pharmaceutical Development and Commercialization and is overseen by an academic steering committee.

The ethics committee at each site approved the protocol (available with the full text of this article at NEJM.org) before trial initiation. All the patients provided written informed consent. The trial was conducted in accordance with the trial protocol, the International Council for Harmonisation guidelines for Good Clinical Practice, ethical principles of the International Declaration of Helsinki, the Council for International Organizations of Medical Sciences guidelines, and applicable laws and regulations. The first author wrote the first draft of the manuscript and had access to the data. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol and contributed to the development and revision of the manuscript and approved submitting it for publication.

Patients were randomized on a 1:1 basis to receive subcutaneous sibeprenlimab at a dose of 400 mg or placebo every 4 weeks to week 100 (26 doses). Randomization was stratified according to screening tests of the 24-hour urinary protein-to-creatinine ratio (≤2 vs. >2, with both protein and creatinine levels measured in grams), screening eGFR (30 to 44 ml per minute per 1.73 $m^2$ of body-surface area vs. ≥45 ml per minute per 1.73 $m^2$ calculated with the 2021 Chronic Kidney Disease Epidemiology creatinine equation),[18] and the use of sodium–glucose cotransporter 2 inhibitors at randomization (yes vs. no) (see Fig. S1 in the Supplementary Appendix, available at NEJM.org).[19] Details of randomization are shown in the Supplementary Appendix.

### Patients

Adults with biopsy-confirmed IgA nephropathy, a 24-hour urinary protein-to-creatinine ratio of 0.75 or higher or 24-hour urinary protein excre-

tion of 1.0 g per day or higher, and eGFR of 30 ml or more per minute per 1.73 $m^2$ at screening were eligible for the main trial cohort. Treatment with a stable and maximally tolerated dose of an angiotensin-converting–enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) for at least 3 months before screening was generally required. Patients in whom therapy with an ACE inhibitor or ARB caused unacceptable side effects were eligible if they were otherwise receiving care that was concordant with applicable IgA nephropathy guidelines.[20] Patients who were receiving stable sodium–glucose cotransporter 2 inhibitor therapy that began at least 3 months before screening were eligible. Complete eligibility criteria are shown in the Supplementary Appendix.

### PROCEDURES

Sibeprenlimab at a dose of 400 mg or matching placebo was administered by subcutaneous injection every 4 weeks. Two urine collections for 24-hour urinary protein-to-creatinine ratio analysis and one first-morning-void collection for a spot urinary protein-to-creatinine ratio analysis within a 7-day window were obtained at scheduled visits.

### END POINTS AND ASSESSMENTS

The primary efficacy end point in this interim analysis was the 24-hour urinary protein-to-creatinine ratio at 9 months as compared with baseline. The key secondary end point of annualized eGFR slope estimated over 24 months currently remains blinded to preserve ongoing trial integrity and is not reported here. The secondary end points presented here include safety (adverse events that emerged during the treatment period) and pharmacodynamic markers (change in total serum IgA, IgG, and IgM levels). Exploratory end points included the change in 24-hour urinary protein-to-creatinine ratio at 12 months, change in spot urinary protein-to-creatinine ratio, hematuria (dipstick test results), serum galactose-deficient IgA1 level, serum concentrations of free APRIL, and remission of proteinuria (urine total protein <0.5 g per day at 12 months). Predefined subgroup analyses of the primary end point were performed as described in the Supplementary Appendix.

### STATISTICAL ANALYSIS

The sample-size calculations showed that at least 450 patients assigned to the two trial groups in a 1:1 ratio would be required to provide the trial with greater than 90% power to detect a 30% reduction in the geometric mean 24-hour urinary protein-to-creatinine ratio and a 2.1 ml per minute per 1.73 $m^2$ between-group difference in the eGFR annualized slope. The primary end point of the 24-hour urinary protein-to-creatinine ratio was planned to be assessed when at least 62.5% of the patients in the main cohort had the opportunity to complete the 24-hour urinary protein-to-creatinine ratio evaluation at 9 months. This end point provided the trial with 91% power for the between-group comparison of 24-hour urinary protein-to-creatinine ratio with a prespecified two-sided alpha of 0.035 at the interim analysis.

The primary estimand was the treatment effect evaluated on the basis of the ratio of 24-hour urinary protein-to-creatinine ratio at 9 months as compared with baseline. Data from patients who discontinued sibeprenlimab or placebo were collected after early discontinuation and were used for analysis. Data collected after the initiation of confounding medications or therapies were treated as missing. In cases of transplantation, dialysis, or death due to kidney disease, data were imputed with the worst possible value across trial groups. At the conclusion of each data-handling scenario, missing 9-month 24-hour urinary protein-to-creatinine ratio values were imputed for each trial group with multiple imputation according to the missing-at-random assumption.

An analysis of covariance model was used for the primary end point to compare the effect of treatment on the 24-hour urinary protein-to-creatinine ratio. Owing to the skewed distribution of the 24-hour urinary protein-to-creatinine ratio, the response variable was the natural log-transformed ratio of the 24-hour urinary protein-to-creatinine ratio at 9 months to the 24-hour urinary protein-to-creatinine ratio at baseline. The model was fitted with trial group and the log-transformed baseline 24-hour urinary protein-to-creatinine ratio; sodium–glucose cotransporter 2 inhibitor use and eGFR were used as stratification factors for randomization. Sensitivity analyses were performed to assess the robustness of assumptions used for data handling (Fig. S2 and Table S1).

Spot analysis of urinary protein-to-creatinine ratio was conducted with the use of a mixed model for repeated measures. Proteinuric remission was analyzed with a logistic-regression

model. Demographic and baseline characteristics, safety, and pharmacodynamic markers were summarized with descriptive statistics.

Confidence intervals from modeling or descriptive statistics have not been adjusted for multiplicity and should not be used in place of hypothesis testing. Additional details regarding the definition of the data set, intercurrent events and estimand, handling of missing data, sensitivity analysis, and type 1 error control are available in the Supplementary Appendix.

## RESULTS

### PATIENTS

A total of 901 patients were assessed for eligibility; 510 were assigned to the main trial cohort (259 to receive sibeprenlimab and 251 to receive placebo). Another 371 patients did not qualify owing to inclusion or exclusion criteria (36.8%), patient withdrawal (0.8%), physician decision (0.2%), protocol deviation (0.1%), adverse event (0.1%), or another reason (3.9%). The present analysis reports on the first 320 patients in the main cohort (152 who received sibeprenlimab and 168 who received placebo) after completion of the prespecified interim-analysis period (data cutoff, September 4, 2024). An additional 20 patients (8 who received sibeprenlimab and 12 who received placebo) with baseline eGFR levels that were between 20 and 29 ml per minute per 1.73 $m^2$ (indicating stage 4 chronic kidney disease) underwent randomization in an exploratory cohort, results from which will be reported separately.

Baseline characteristics were similar in the two groups in the interim analysis (Table 1 and Table S2) and similar to those of the overall trial population (Tables S3 and S4). In the interim analysis, 62.5% of patients were men, 59.1% were Asian, and 97.5% and 40.0% reported pretrial use of renin–angiotensin system inhibitors and sodium–glucose cotransporter 2 inhibitors, respectively. The median age was 42 years, the mean eGFR was 63.4 ml per minute per 1.73 $m^2$, and the median 24-hour urinary protein-to-creatinine ratio was 1.25. The median time from initial kidney biopsy to randomization was 1.5 years. The trial population was generally representative of persons with a diagnosis of IgA nephropathy (Table S5).

At the interim-analysis cutoff date, 25 of 510 patients had discontinued the trial regimen, including 22 (9 in the sibeprenlimab group and 13 in the placebo group) in the interim-analysis population. The reasons for discontinuation of the trial regimen included patient decision (in 9 patients), physician decision (in 3), received prohibited medication (in 3), adverse event (in 2), progressive disease (in 2), protocol-specific withdrawal criterion met (in 1), and other reasons (in 2) (Fig. S3). A total of 18 patients in the main cohort had withdrawn from the trial as of the interim-analysis cutoff date, primarily owing to patient decision (in 13), including 2 patients who withdrew owing to an adverse event (respiratory tract infection and upper respiratory tract infection or presumed pneumonia, both assessed as being nonsevere and nonserious).

### EFFECTS ON PROTEINURIA

At week 40, there was a 50.2% reduction in the 24-hour urinary protein-to-creatinine ratio from baseline among patients assigned to receive sibeprenlimab (95% confidence interval [CI], 44.0 to 55.6) as compared with a 2.1% increase (95% CI, −8.5 to 13) in patients assigned to receive placebo, corresponding to an adjusted geometric least-squares mean 24-hour urinary protein-to-creatinine ratio that was 51.2% (96.5% confidence interval [CI], 42.9 to 58.2) lower with sibeprenlimab than with placebo (P<0.001) (Fig. 1A). At 12 months (week 52), the 24-hour urinary protein-to-creatinine ratio as compared with baseline was 56.6% lower (95% CI, 50.8 to 61.7) in patients receiving sibeprenlimab as compared with 5.1% lower (95% CI, −6.7 to 15.7) in patients receiving placebo, corresponding to a placebo-adjusted difference in the 24-hour urinary protein-to-creatinine ratio of 54.3% (95% CI, 46.4 to 60.9). Results of prespecified sensitivity analyses were consistent with the primary analysis (Table S6).

With regard to spot assessment of urinary protein-to-creatinine ratio levels according to visit, the mixed model for repeated measures showed that separation between the groups occurred rapidly, with a substantial difference observed at 8 weeks and sustained through 12 months (Fig. 1B). Patients receiving sibeprenlimab had a 45.6% (95% CI, 37.2 to 52.9) lower spot urinary protein-to-creatinine ratio at month 9 than at baseline, as compared with a 14.4% (95% CI, 0.1 to 30.7) higher level with placebo,

**Table 1. Demographic and Clinical Characteristics of the Interim-Analysis Population at Baseline.***

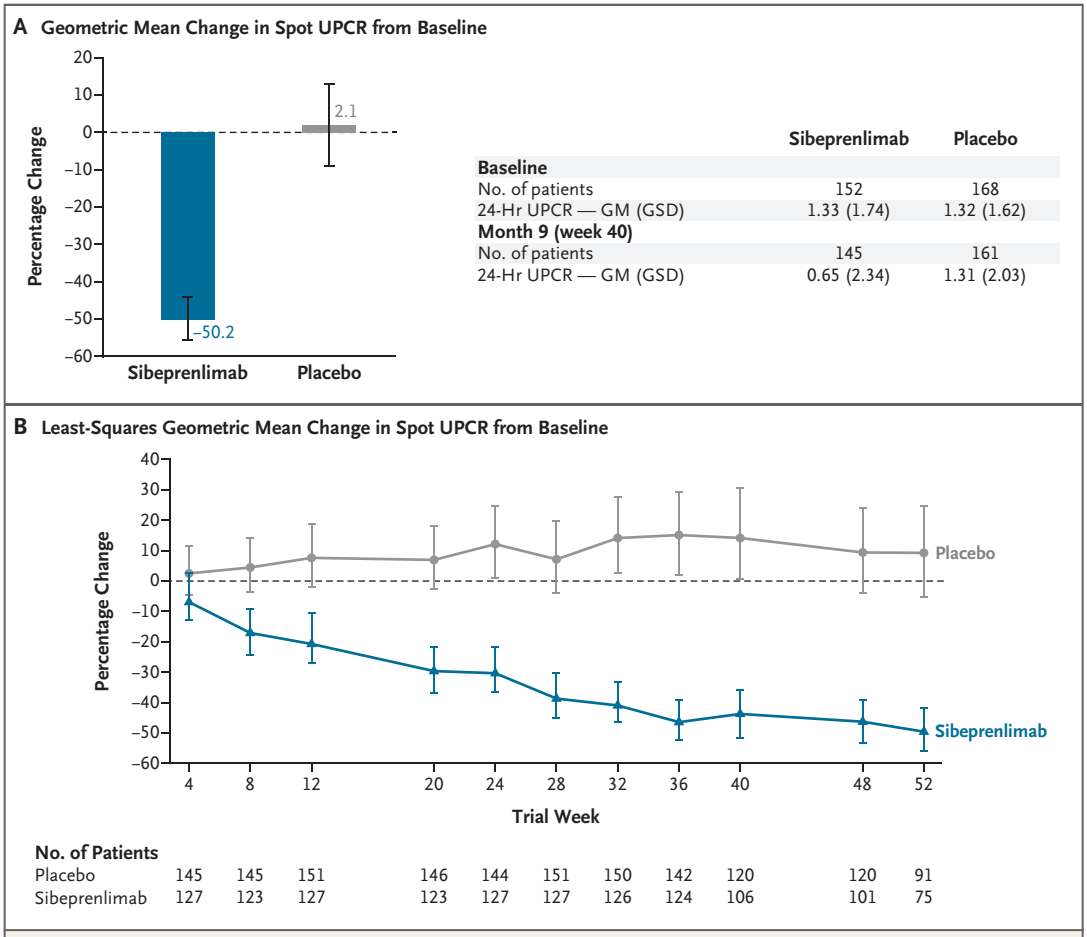
| Characteristic | Sibeprenlimab (N=152) | Placebo (N=168) |
|---|---|---|
| Median age (range) — yr | 42.0 (18–75) | 43.0 (18–83) |
| Sex — no. (%) | | |
| Male | 100 (65.8) | 100 (59.5) |
| Female | 52 (34.2) | 68 (40.5) |
| Race — no. (%)† | | |
| Asian | 94 (61.8) | 95 (56.5) |
| White | 55 (36.2) | 66 (39.3) |
| Other | 3 (2.0) | 7 (4.2) |
| Ethnic group — no. (%)† | | |
| Hispanic or Latinx | 16 (10.5) | 22 (13.1) |
| Not Hispanic or Latinx | 132 (86.8) | 141 (83.9) |
| Other (including unknown) | 4 (2.6) | 5 (3.0) |
| Region — no. (%)‡ | | |
| North America | 22 (14.5) | 21 (12.5) |
| South America | 11 (7.2) | 15 (8.9) |
| Europe | 30 (19.7) | 36 (21.4) |
| East Asia | 43 (28.3) | 48 (28.6) |
| South Asia or Southeast Asia | 46 (30.3) | 48 (28.6) |
| Mean body-mass index§ | 28.0±6.1 | 26.7±4.9 |
| Mean blood pressure — mm Hg | | |
| Systolic blood pressure | 124.5±11.3 | 123.1±11.4 |
| Diastolic blood pressure | 77.8±8.1 | 78.7±8.0 |
| Median time from initial biopsy to randomization (range) — yr | 1.30 (0.10–23.70) | 1.85 (0.00–34.00) |
| 24-Hr urinary protein-to-creatinine ratio¶‖ | | |
| Geometric mean | 1.33±1.74 | 1.32±1.63 |
| Median (range) | 1.22 (0.49–6.69) | 1.28 (0.50–5.46) |
| eGFR — ml/min/1.73 $m^2$¶ | | |
| Mean | 63.49±24.40 | 63.36±25.34 |
| Median (range) | 57.5 (25.0–131.0) | 60.0 (27.0–129.0) |
| Hematuria — no. (%)** | | |
| Negative | 33 (21.7) | 49 (29.2) |
| Positive | 119 (78.3) | 119 (70.8) |
| Previous use of immunosuppressive drugs — no. (%)†† | 6 (3.9) | 6 (3.6) |
| Background regimen — no. (%) | | |
| ACE inhibitor or ARB or both | 149 (98.0) | 163 (97.0) |
| Sodium–glucose cotransporter 2 inhibitor | 56 (36.8) | 72 (42.9) |

* Plus–minus values are means ±SD. The interim-analysis population comprised the first 320 patients who had the opportunity to complete the 9-month evaluation of the 24-hour urinary protein-to-creatinine ratio, which was based on 24-hour urine collection, with protein and creatinine both measured in grams. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, and eGFR estimated glomerular filtration rate.
† Race and ethnic group were reported by investigators at the trial sites.
‡ North America includes Canada and the United States; South America includes Argentina and Brazil; Europe includes Belgium, the Czech Republic, Germany, Spain, France, the United Kingdom, Greece, Croatia, Hungary, Israel, Italy, Holland, Poland, and Portugal; East Asia includes China, Hong Kong, Japan, South Korea, and Taiwan; South or Southeast Asia includes Australia, India, Sri Lanka, Malaysia, the Philippines, Singapore, Thailand, and Vietnam.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.
¶ Baseline measurements were defined as the last available assessment at or before the first dose of sibeprenlimab, unless stated otherwise.
‖ Urinary total protein was based on 24-hour urine collection.
** Results shown are from dipstick test. Positive hematuria is defined as trace, 1+, 2+, or 3+.
†† Previous use included systemic glucocorticoids and other immunosuppressive drugs or therapies.

for a between-group difference of 52.4% (95% CI, 42.7 to 60.5). Results of efficacy assessments for change in 24-hour urinary albumin-to-creatinine ratio were consistent with the proteinuria findings (Table S7).

### SUBGROUP ANALYSES FOR PROTEINURIA

The effects of sibeprenlimab on 24-hour urinary protein-to-creatinine ratio according to prespecified subgroups showed consistency across sex, ethnic group, region, race, age, screening 24-hour




| | Sibeprenlimab | Placebo |
|---|---|---|
| **Baseline** | | |
| No. of patients | 152 | 168 |
| 24-Hr UPCR — GM (GSD) | 1.33 (1.74) | 1.32 (1.62) |
| **Month 9 (week 40)** | | |
| No. of patients | 145 | 161 |
| 24-Hr UPCR — GM (GSD) | 0.65 (2.34) | 1.31 (2.03) |

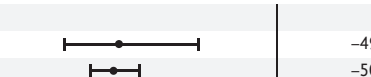
**Figure 1. Change from Baseline in Urinary Protein-to-Creatinine Ratio.**

The full-analysis population comprises patients who were in the interim-analysis population (the first 62.5% of patients who underwent randomization, had a baseline 24-hour urinary protein-to-creatinine ratio [UPCR] evaluation, and had the opportunity to complete the 9-month [40-week] 24-hour UPCR evaluation). In Panel A, the percentage reduction of 24-hour UPCR at month 9 is compared to baseline with the use of analysis of covariance (ANCOVA). The percentage reduction was calculated using the following formula: (−1) × (1−the geometric mean [GM] of the 24-hour UPCR estimated from the ANCOVA model) × 100%. The error bars indicate the 95% confidence interval (CI) of the GM. The placebo-adjusted treatment effect is 51.2% (96.5% CI, 42.9–58.2; P<0.001). The 95% confidence intervals shown in Panels A and B correspond to the treatment-specific reductions, whereas the 96.5% confidence interval shown in Panel A corresponds to the between-group difference aligned with the predefined split alpha of 0.035 used for testing the 24-hour UPCR end point in the interim analysis. For the 24-hour UPCR, both protein and creatinine are measured in grams. Panel B shows a line plot (generated from a mixed model for repeated measures) of spot UPCR results by visit as compared with baseline. Error bars indicate 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing. GSD denotes geometric standard deviation.

urinary protein-to-creatinine ratio (≤2 vs. >2), eGFR (30 to 44 ml per minute per 1.73 $m^2$ vs. ≥45 ml per minute per 1.73 $m^2$), and background use of sodium–glucose cotransporter 2 inhibitors. Consistency was also observed in baseline histopathologic activity and medication history, including previous use of immunosuppressive therapy (Fig. 2 and Fig. S4).

**A Change in 24-Hour UPCR from Baseline at 9 Months, According to Demographic Characteristics**

| Subgroup | Sibeprenlimab | Placebo | Percentage Change, Sibeprenlimab vs. Placebo (95% CI) |
|---|---|---|---|
| | *no. of patients* | | |
| Ethnic group | | | |
| Hispanic or Latinx | 16 | 22 | −49.3 (−65.9 to −24.4) |
| Not Hispanic or Latinx | 132 | 141 | −50.9 (−57.9 to −42.7) |
| Sex at birth | | | |
| Male | 100 | 100 | −51.9 (−60.4 to −41.6) |
| Female | 52 | 68 | −50.3 (−59.8 to −38.5) |
| Age | | | |
| ≤40 yr | 69 | 68 | −51.8 (−60.3 to −41.5) |
| >40 yr | 83 | 100 | −51.8 (−60.7 to −40.9) |
| Race | | | |
| Asian | 94 | 95 | −53.8 (−61.8 to −44.2) |
| White | 55 | 66 | −45.8 (−56.6 to −32.4) |
| Geographic region | | | |
| North America | 22 | 21 | −25.6 (−48.6 to 7.5) |
| South America | 11 | 15 | −37.1 (−60.8 to 1.2) |
| Europe | 30 | 36 | −54.1 (−66.2 to −37.7) |
| East Asia | 43 | 48 | −56.5 (−66.7 to −43.3) |
| South and Southeast Asia | 46 | 48 | −56.5 (−67.7 to −41.4) |




**B Change in 24-Hour UPCR from Baseline over 9 Months, According to Stratification Factors**

| Subgroup | Sibeprenlimab | Placebo | Percentage Change, Sibeprenlimab vs. Placebo (95% CI) |
|---|---|---|---|
| | *no. of patients* | | |
| 24-Hr UPCR based on IRT record | | | |
| ≤2.0 g/g | 116 | 130 | −45.9 (−53.9 to −36.6) |
| >2.0 g/g | 36 | 38 | −64.7 (−74.4 to −51.3) |
| Estimated GFR based on IRT record | | | |
| 30–44 ml/min/1.73 $m^2$ | 37 | 43 | −44.7 (−59.4 to −24.5) |
| ≥45 ml/min/1.73 $m^2$ | 115 | 125 | −52.6 (−59.8 to −44.2) |
| Screening SGLT2i based on IRT record | | | |
| No | 98 | 96 | −50.0 (−59.0 to −39.1) |
| Yes | 54 | 72 | −52.9 (−61.8 to −42.0) |

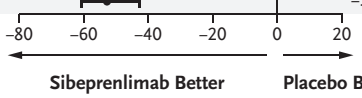



**Figure 2. Interim Subgroup Analyses of 24-Hr UPCR at 9 Months (Full Analysis Population).**

Panel A shows a forest plot for the subgroup analysis of the 24-hour UPCR at month 9 as compared with baseline according to demographic characteristics (including ethnic group, sex at birth, age group, and region). Panel B shows a forest plot for the subgroup analysis of the 24-hour UPCR at month 9 as compared with baseline according to stratification factors (including 24-hour UPCR, estimated glomerular filtration rate [eGFR], and sodium–glucose cotransporter 2 inhibitor [SGLT2i]). The percentage change is based on the ratio of sibeprenlimab to placebo. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing. IRT denotes interactive response technology.

### REMISSION OF PROTEINURIA AND RESOLUTION OF HEMATURIA

Among participants for whom there were nonmissing measurements of urine total protein and hematuria, remission of proteinuria (total urinary protein of <0.5 g per day at 12 months) occurred in 34 of 99 patients (34.3%; 95% CI, 25.1 to 44.6) who received sibeprenlimab as compared with 15 of 118 patients (12.7%; 95% CI, 7.3 to 20.1) who received placebo. At baseline, 119 of 152 patients in the sibeprenlimab group (78.3%) and 119 of 168 patients who received placebo (70.8%) had hematuria (trace results or greater on a dipstick test). At week 48, these percentages had decreased to 22 of 111 in the sibeprenlimab group (19.8%) and 89 of 129 in the placebo group (69.0%) (Fig. S5).

### BIOMARKERS

In the sibeprenlimab group, levels of serum galactose-deficient IgA1 decreased by 44.6% (95% CI, 42.3 to 46.9) at week 4, by 63.6% (95% CI, 59.4 to 67.7) at week 24, and by 67.1% (95% CI, 62.8 to 71.3) at week 48 (Fig. 3A). APRIL levels

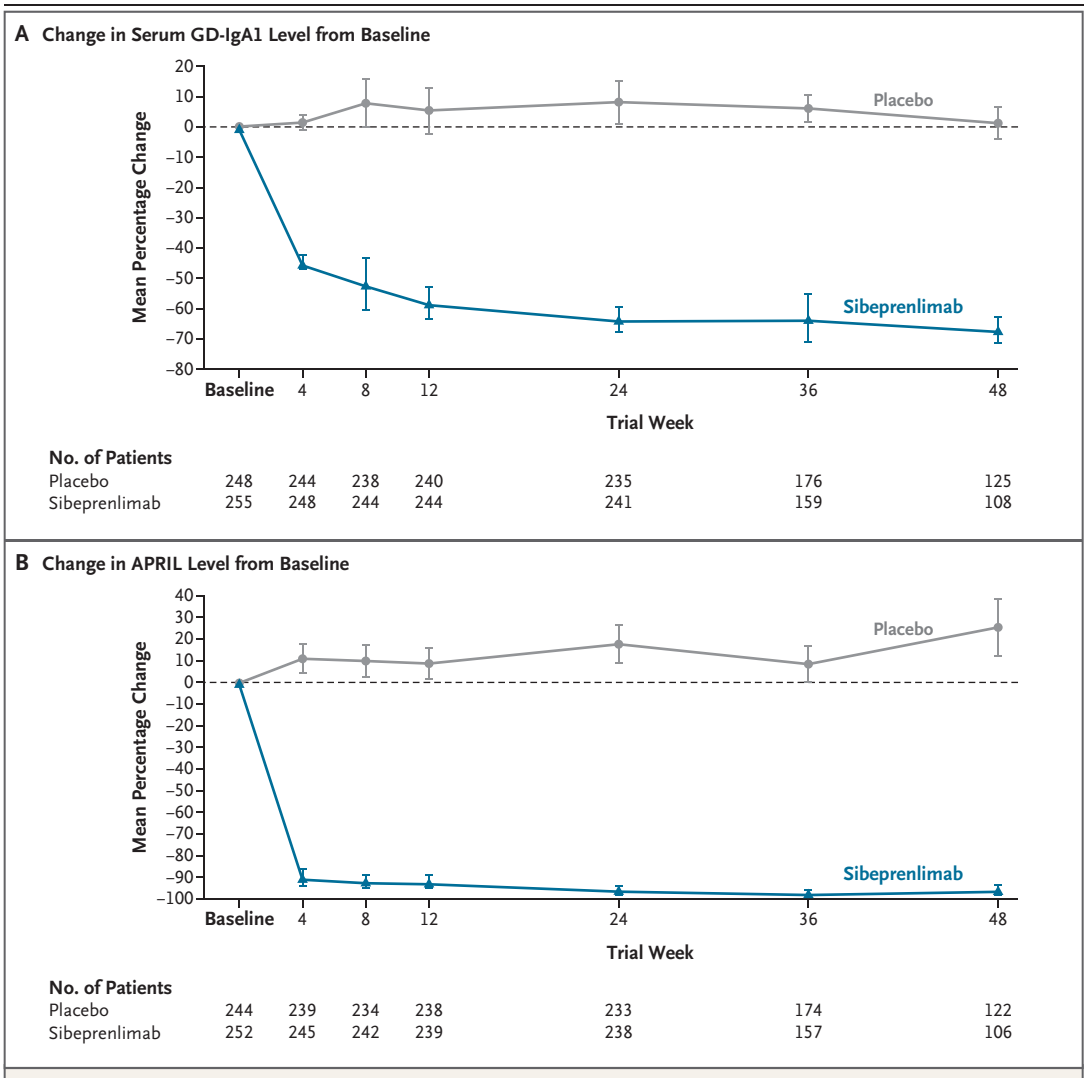



**Figure 3. Change in Serum GD-IgA1 and Serum APRIL Levels in the Pharmacodynamic Population over Time.**

The pharmacodynamic population consisted of all the participants who received at least one dose of sibeprenlimab or placebo and who had a baseline and at least one postbaseline evaluable (nonmissing and interpretable) pharmacodynamic measurement. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing. APRIL denotes the cytokine A proliferation-inducing ligand.

**Table 2. Adverse Events Occurring during the Treatment Period in the Safety Population.***

| Event | Sibeprenlimab (N=259) | Placebo (N=251) |
|---|---|---|
| | *no. of patients (%)* | |
| Any adverse event occurring during treatment period† | 192 (74.1) | 206 (82.1) |
| Adverse event related to sibeprenlimab or placebo | 75 (29.0) | 67 (26.7) |
| Event occurring in ≥5% of patients in either trial group | | |
| Injection-site erythema | 34 (13.1) | 30 (12.0) |
| Injection-site pain | 26 (10.0) | 23 (9.2) |
| Injection-site swelling | 16 (6.2) | 13 (5.2) |
| Pyrexia | 14 (5.4) | 10 (4.0) |
| Coronavirus disease 2019 | 25 (9.7) | 17 (6.8) |
| Influenza | 21 (8.1) | 16 (6.4) |
| Nasopharyngitis | 32 (12.4) | 25 (10.0) |
| Upper respiratory tract infection | 38 (14.7) | 35 (13.9) |
| Back pain | 17 (6.6) | 14 (5.6) |
| Any serious adverse event occurring during treatment period‡ | 9 (3.5) | 11 (4.4) |
| Any serious adverse event related to sibeprenlimab or placebo | 1 (0.4) | 1 (0.4) |
| Any severe adverse event occurring during treatment period | 4 (1.5) | 8 (3.2) |
| Any adverse event leading to discontinuation of sibeprenlimab or placebo | 1 (0.4) | 4 (1.6) |
| Death | 0 | 0 |

* The safety population consisted of all the participants who received at least one dose of sibeprenlimab or placebo.
† Adverse events are coded according to the *Medical Dictionary for Regulatory Activities* (MedDRA), version 27.0.
‡ A serious adverse event is any event that results in death, is life-threatening, causes persistent or substantial disability or incapacity, substantially disrupts normal life functions, or results in or prolongs hospitalization (excluding social or prescheduled admissions, with the reason for hospitalization reported whenever possible). A serious adverse event also includes congenital anomaly or birth defect or other medically significant events which, in the investigator's judgment, may jeopardize the patient and lead to medical or surgical intervention to prevent a serious outcome listed above. Participants with multiple adverse events are counted only once per specific MedDRA preferred term. Participants with multiple adverse events in multiple organ system classes are counted only once toward the total.

with sibeprenlimab were 90.2% lower than baseline (95% CI, 86.5 to 93.9) at week 4 and 95.8% lower at week 48 (95% CI, 93.9 to 97.7) (Fig. 3B). At week 48, serum IgA levels had decreased in patients receiving sibeprenlimab by 68.8% (95% CI, 67.2 to 70.5), IgG levels had decreased by 35.0% (95% CI, 32.8 to 37.3), and IgM levels had decreased by 74.5% (95% CI, 73.1 to 75.9) (Fig. S6). Minimal changes were observed with placebo.

### SAFETY

At the time of the interim-analysis data cutoff, the incidence of adverse events that occurred during the treatment period in the safety population (510 patients) was similar in the two groups — 74.1% with sibeprenlimab and 82.1% with placebo (Table 2), with most adverse events reported to be mild to moderate in severity. The adverse events that were most commonly reported during treatment (occurring in at least 2% of the patients in the sibeprenlimab group) were defined according to the *Medical Dictionary for Regulatory Activities*, version 27.0, system organ class of infections and infestations (in 39.0% of patients in the sibeprenlimab group and 32.7% in the placebo group). The most common events were upper respiratory tract infections (14.7% with sibeprenlimab and 13.9% with placebo) and nasopharyngitis (12.4% and 10.0%, respectively). In the sibeprenlimab group, 9.7% of patients had coronavirus 2019 (Covid-19) infection as compared with 6.8% in the placebo group; influenza was reported in 8.1% and 6.4%, respectively. Nine patients in the sibeprenlimab

group had postbaseline IgG levels of less than 400 mg per deciliter; two of those patients had adverse events (moderate Covid-19 in one and mild urinary tract infection in the other) that occurred during treatment and resolved without dose modification.

Adverse events that occurred during the treatment period and led to discontinuation of the trial regimen were reported in 1 patient (0.4%) in the sibeprenlimab group and 4 patients (1.6%) in the placebo group. Serious adverse events (Table S8) and severe adverse events (Table S9) that occurred during the treatment period were reported in 9 patients (3.5%) and 4 patients (1.5%), respectively, in the sibeprenlimab group and in 11 patients (4.4%) and 8 patients (3.2%), respectively, in the placebo group. No deaths occurred.

## DISCUSSION

The progressive nature of IgA nephropathy in patients with elevated proteinuria despite background therapy places most of these patients at risk for progression of chronic kidney disease and kidney failure within their lifetime.[5,6] Therefore, effective therapies targeting the underlying immune drivers of nephron loss are urgently needed. In this trial, we showed that sibeprenlimab treatment was associated with a significant placebo-adjusted reduction (51.2%) in the 24-hour urinary protein-to-creatinine ratio at 9 months.

Although no direct comparisons are currently available, the 51.2% relative reduction in proteinuria that was observed in this trial appeared to be at least as large as those reported with currently approved therapies, including budesonide,[21] sparsentan,[22] atrasentan,[23] and iptacopan.[24] These results are consistent with those reported in our phase 2 trial,[15] in which a comparable intravenous dose of sibeprenlimab (4 mg per kilogram monthly) reduced proteinuria by 48%. Despite substantial reductions in proteinuria levels associated with all the approved agents to date, average proteinuria levels after treatment are still indicative of ongoing risk of disease progression.[25-28]

The findings of this interim analysis appeared consistent across subgroups. Reductions in proteinuria were observed regardless of the use of sodium–glucose cotransporter 2 inhibitors at baseline. Hematuria resolution and remission of proteinuria were also noted in a greater percentage of patients who received sibeprenlimab than in those who received placebo. Emerging evidence supports targeting proteinuria of less than 0.5 g per day to attain better long-term kidney outcomes[5,6] and suggests that remission of both proteinuria and hematuria is associated with greater kidney survival.[29] We speculate that the present results suggest that sibeprenlimab may protect kidney function.

The magnitude of the reduction in proteinuria across disease activity and chronicity and the decreases in galactose-deficient IgA1 and APRIL levels we observed with sibeprenlimab for the treatment of IgA nephropathy by targeting putative underlying immune drivers appear potentially promising. Thus, we postulate that sibeprenlimab may be more specific than therapies with broader immunosuppressive effect, such as glucocorticoid therapy, therapies addressing glomerular inflammation through the alternative complement pathway (e.g., iptacopan), and those with primarily hemodynamic effects on glomeruli (e.g., sodium–glucose cotransporter 2 inhibitors or endothelin antagonists). A renal-biopsy substudy of this trial and a phase 2b study (NCT06740526) are currently underway to evaluate the histopathological changes that promote further understanding of potential disease-modifying effects of sibeprenlimab.

In this trial, total IgA and IgM levels were reduced by approximately 70% with sibeprenlimab, whereas IgG levels were reduced by 35%. Despite these reductions, the safety profile of sibeprenlimab showed no apparent evidence of adverse effects at the time of analysis. Although a numerical excess of Covid-19 and influenza was observed in patients who received sibeprenlimab, there were no life-threatening cases of either infection nor was there evidence of an increase in risk of other more serious infections. However, data on long-term safety are needed and further evaluation is planned in the final report from this trial and the phase 2–3 open-label long-term extension study (NCT05248659). This trial is ongoing, and the evaluation of the efficacy of sibeprenlimab in preserving kidney function as well as safety over 24 months is planned.

The present large trial in IgA nephropathy patients is demographically and geographically diverse and reflective of IgA nephropathy epide-

miology. Most of the patients were Asian — a population in whom the disease follows a more aggressive course[30] — although similar effects were observed in non-Asian patients.

This analysis has certain limitations. Because we are reporting an interim analysis of an ongoing trial, the effects of sibeprenlimab on eGFR and long-term safety outcomes are not yet available. The median time from kidney biopsy was 1.5 years, limiting the assessment of pretreatment biopsy features on response. Further studies are also needed to clarify the role of APRIL inhibition relative to APRIL–BAFF (B-cell activating factor) dual blockade or other B-cell–targeted approaches.

In this prespecified interim analysis of the VISIONARY trial, sibeprenlimab resulted in a significant reduction in proteinuria in patients with IgA nephropathy.

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## REFERENCES

1. Knoppova B, Reily C, King RG, Julian BA, Novak J, Green TJ. Pathogenesis of IgA nephropathy: current understanding and implications for development of disease-specific treatment. J Clin Med 2021; 10:4501.
2. Caster DJ, Abner CW, Walker PD, et al. Clinicopathological characteristics of adult IgA nephropathy in the United States. Kidney Int Rep 2023;8:1792-800.
3. Rajasekaran A, Julian BA, Rizk DV. IgA nephropathy: an interesting autoimmune kidney disease. Am J Med Sci 2021; 361:176-94.
4. Cheung CK, Barratt J, Liew A, Zhang H, Tesar V, Lafayette R. The role of BAFF and APRIL in IgA nephropathy: pathogenic mechanisms and targeted therapies. Front Nephrol 2024;3:1346769.
5. Pitcher D, Braddon F, Hendry B, et al. Long-term outcomes in IgA nephropathy. Clin J Am Soc Nephrol 2023;18:727-38.
6. Sim JJ, Chen Q, Cannizzaro N, et al. CKD progression, kidney failure, and mortality among US patients with IgA nephropathy. Nephrol Dial Transplant 2025 April 30 (Epub ahead of print).
7. Faucon A-L, Lundberg S, Lando S, et al. Albuminuria predicts kidney events in IgA nephropathy. Nephrol Dial Transplant 2025;40:465-74.
8. Stamellou E, Nadal J, Hendry B, et al. Long-term outcomes of patients with IgA nephropathy in the German CKD cohort. Clin Kidney J 2024;17(8):sfae230.
9. Suzuki H, Kiryluk K, Novak J, et al. The pathophysiology of IgA nephropathy. J Am Soc Nephrol 2011;22:1795-803.
10. Inker LA, Mondal H, Greene T, et al. Early change in urine protein as a surrogate end point in studies of IgA nephropathy: an individual-patient meta-analysis. Am J Kidney Dis 2016;68:392-401.
11. Thompson A, Carroll K, Inker LA, et al. Proteinuria reduction as a surrogate end point in trials of IgA nephropathy. Clin J Am Soc Nephrol 2019;14:469-81.
12. Mathur M, Barratt J, Suzuki Y, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of VIS649 (sibeprenlimab), an APRIL-neutralizing $IgG_2$ monoclonal antibody, in healthy volunteers. Kidney Int Rep 2022;7:993-1003.
13. Myette JR, Kano T, Suzuki H, et al. A Proliferation Inducing Ligand (APRIL) targeted antibody is a safe and effective treatment of murine IgA nephropathy. Kidney Int 2019;96:104-16.
14. Chacko B, Mathur M, Rizk DV. APRIL: a key factor in the pathogenesis of IgA nephropathy. Kidney News 2024;16(1):11-2 (https://www.kidneynews.org/view/journals/kidney-news/16/1/article-p11_7.xml).
15. Mathur M, Barratt J, Chacko B, et al. A phase 2 trial of sibeprenlimab in patients with IgA nephropathy. N Engl J Med 2024; 390:20-31.
16. ClinicalTrials.gov. Visionary study: phase 3 trial of sibeprenlimab in immunoglobulin A nephropathy (IgAN). 2025 (https://clinicaltrials.gov/study/NCT05248646).
17. Zhang X, Wang Y, Yarbrough J, et al. Safety, pharmacokinetics, and pharmacodynamics of subcutaneous sibeprenlimab in healthy participants. Clin Pharmacol Drug Dev 2023;12:1211-20.
18. Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C–based equations to estimate GFR without race. N Engl J Med 2021;385:1737-49.
19. Perkovic V, Barratt J, Lafayette R, et al. Evaluating sibeprenlimab in IgA nephropathy — rationale and baseline data from the VISIONARY trial. Kidney Int Rep. October 1, 2025 (https://www.kireports.org/article/S2468-0249(25)00605-9/fulltext).

**20.** Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. Kidney Int 2021;100:S1-S276.
**21.** Barratt J, Lafayette R, Kristensen J, et al. Results from part A of the multi-center, double-blind, randomized, placebo-controlled NefIgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy. Kidney Int 2023;103:391-402.
**22.** Heerspink HJL, Radhakrishnan J, Alpers CE, et al. Sparsentan in patients with IgA nephropathy: a prespecified interim analysis from a randomised, double-blind, active-controlled clinical trial. Lancet 2023;401:1584-94.
**23.** Heerspink HJL, Jardine M, Kohan DE, et al. Atrasentan in patients with IgA nephropathy. N Engl J Med 2025;392:544-54.
**24.** Perkovic V, Barratt J, Rovin B, et al. Alternative complement pathway inhibition with iptacopan in IgA nephropathy. N Engl J Med 2025;392:531-43.
**25.** Tarpeyo (budesonide): highlights of prescribing information. Stockholm: Calliditas Therapeutics, 2021 (https://www.tarpeyo.com/prescribinginformation.pdf).
**26.** Vanrafia (atrasentan): highlights of prescribing information. East Hanover, NJ: Novartis Pharmaceuticals, 2025 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219208s000lbl.pdf).
**27.** Fabhalta (iptacopan): highlights of prescribing information. East Hanover, NJ: Novartis Pharmaceuticals, 2025 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/218276s001lbl.pdf).
**28.** Filspari (sparsentan): highlights of prescribing information. San Diego, CA: Travere Therapeutics, 2025 (https://filspari.com/igan/filspari-prescribing-information.pdf).
**29.** Fang X, Bi X, Xiao T, et al. Early post-treatment remission of proteinuria is associated with long-term prognosis in patients with immunoglobulin A nephropathy. Int Urol Nephrol 2025;57:3451-60.
**30.** Yeo SC, Goh SM, Barratt J. Is immunoglobulin A nephropathy different in different ethnic populations? Nephrology (Carlton) 2019;24:885-95.