ORIGINAL ARTICLE

A Phase 2 Trial of Sibeprenlimab in Patients with IgA Nephropathy

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ABSTRACT

BACKGROUND

A proliferation-inducing ligand (APRIL) is implicated in the pathogenesis of IgA nephropathy. Sibeprenlimab is a humanized IgG2 monoclonal antibody that binds to and neutralizes APRIL.

METHODS

In this phase 2, multicenter, double-blind, randomized, placebo-controlled, parallel-group trial, we randomly assigned adults with biopsy-confirmed IgA nephropathy who were at high risk for disease progression, despite having received standard-care treatment, in a 1:1:1:1 ratio to receive intravenous sibeprenlimab at a dose of 2, 4, or 8 mg per kilogram of body weight or placebo once monthly for 12 months. The primary end point was the change from baseline in the log-transformed 24-hour urinary protein-to-creatinine ratio at month 12. Secondary end points included the change from baseline in the estimated glomerular filtration rate (eGFR) at month 12. Safety was also assessed.

RESULTS

Among 155 patients who underwent randomization, 38 received sibeprenlimab at a dose of 2 mg per kilogram, 41 received sibeprenlimab at a dose of 4 mg per kilogram, 38 received sibeprenlimab at a dose of 8 mg per kilogram, and 38 received placebo. At 12 months, the geometric mean ratio reduction (±SE) from baseline in the 24-hour urinary protein-to-creatinine ratio was 47.2±8.2%, 58.8±6.1%, 62.0±5.7%, and 20.0±12.6% in the sibeprenlimab 2-mg, 4-mg, and 8-mg groups and the placebo group, respectively. At 12 months, the least-squares mean (±SE) change from baseline in eGFR was –2.7±1.8, 0.2±1.7, –1.5±1.8, and –7.4±1.8 ml per minute per 1.73 m^2 in the sibeprenlimab 2-mg, 4-mg, and 8-mg groups and the placebo group, respectively. The incidence of adverse events that occurred after the start of administration of sibeprenlimab or placebo was 78.6% in the pooled sibeprenlimab groups and 71.1% in the placebo group.

CONCLUSIONS

In patients with IgA nephropathy, 12 months of treatment with sibeprenlimab resulted in a significantly greater decrease in proteinuria than placebo. (Funded by Visterra; ENVISION ClinicalTrials.gov number, NCT04287985; EudraCT number, 2019-002531-29.)

IgA nephropathy is the most common cause of primary glomerulonephritis worldwide.[1,2] At least 30% of affected patients have progression to kidney failure within 20 to 30 years after diagnosis, despite having received optimized standard care.[1,3] Standard therapy with nonspecific supportive measures, including treatment for blood-pressure control and treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) for proteinuria, has shown modest efficacy, at best, in reducing the rate of progression of chronic kidney disease (CKD) to end-stage kidney disease, and the efficacy of sodium–glucose cotransporter 2 inhibition is incompletely elucidated.[3,4] Nonspecific immunosuppression with systemic or enteric-coated glucocorticoids has shown efficacy in high-risk persons,[4-7] but benefits generally wane without continued therapy, which is prohibited by safety concerns and the occurrence of bothersome side effects.[4] Thus, a disease-specific targeted treatment that is safe and is effective in delaying disease progression in patients with IgA nephropathy would be of benefit.

A critical stage in the pathogenesis of IgA nephropathy is the production of galactose-deficient IgA1.[8-10] The development of autoantibodies against galactose-deficient IgA1 leads to the formation of circulating immune complexes that deposit in the mesangium of the glomeruli, which triggers an inflammatory response, complement activation, and a dysregulated proliferative response and results in progressively worsening kidney damage.[11-15] Multiple lines of evidence support a key role for a proliferation-inducing ligand (APRIL) in the pathogenesis of IgA nephropathy.[16-22] APRIL, a member of the tumor necrosis factor α superfamily, regulates B-cell–mediated immune responses, including IgA production, through interaction with B-cell maturation antigen,[23] and TACI (transmembrane activator and calcium-modulator and cytophilin-ligand interactor).[24] Blocking APRIL activity presents a potential method of treatment to reduce circulating levels of galactose-deficient IgA1 and associated immune complexes.

Sibeprenlimab (VIS649) is a humanized IgG2 monoclonal antibody that binds to and neutralizes APRIL activity.[25] Preclinical and phase 1 studies have shown reversible, dose-dependent reductions in the serum levels of IgA, galactose-deficient IgA1, IgG, IgM, and APRIL after administration of sibeprenlimab.[25,26] The aim of the current trial was to evaluate the efficacy and safety of different doses of sibeprenlimab in patients with IgA nephropathy who were at high risk for disease progression.

A Quick Take is available at NEJM.org

Methods

Trial Design and Oversight

This phase 2, multicenter, double-blind, randomized, placebo-controlled, multiple-dose, parallel-group trial of sibeprenlimab in adults with IgA nephropathy was conducted at 98 centers across 15 countries (see the Supplementary Appendix, available with the full text of this article at NEJM.org).

Sibeprenlimab or placebo was administered monthly for 12 months as an add-on to standard-care treatment (the highest dose of treatment with an ACE inhibitor or an ARB that was associated with minimal unacceptable side effects). Patients were randomly assigned in a 1:1:1:1 ratio to receive intravenous sibeprenlimab at a dose of 2, 4, or 8 mg per kilogram of body weight or placebo, with the use of an interactive voice-response or Web-response system. Randomization was stratified according to geographic region (Japan vs. the rest of the world), and the rest of the world was further stratified according to the 24-hour urinary protein-to-creatinine ratio (≤2.0 vs. >2.0 g of protein per gram of creatinine) at screening. The sponsor (Visterra), trial personnel, and patients were all unaware of the trial-group assignments.

The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation guidelines for Good Clinical Practice. The institutional review board or ethics committee at each participating center approved the protocol (available at NEJM.org) before initiation of the trial. All the patients provided written informed consent.

Authors who were employed by the sponsor were involved in the design of the trial; the collection, analysis, and interpretation of the data; the writing and reviewing of earlier versions of the manuscript; and the decision to submit the manuscript for publication. The first and penultimate authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

Patients

Eligible patients were 18 years of age or older; had biopsy-confirmed IgA nephropathy; had a

24-hour urinary protein-to-creatinine ratio of at least 0.75 g of protein per gram of creatinine (or a urinary protein level of ≥1.0 g per day); had an estimated glomerular filtration rate (eGFR) of at least 30 ml per minute per 1.73 m^2 of body-surface area (as calculated with the use of the 2009 Chronic Kidney Disease Epidemiology Collaboration equation[27]); had a serum IgG level of at least 700 mg per deciliter, an IgM level of at least 37 mg per deciliter, and an IgA level of at least 70 mg per deciliter; and were receiving the highest stable dose of treatment with an ACE inhibitor or an ARB that resulted in minimal unacceptable side effects, for at least 3 months before screening.

Key exclusion criteria were secondary forms of IgA nephropathy, other coexisting causes of CKD, nephrotic syndrome, type 1 diabetes, uncontrolled type 2 diabetes, uncontrolled blood pressure, receipt of systemic immunosuppressive therapy or systemic glucocorticoid therapy within 16 weeks before initial screening, known chronic infectious disease, and an Oxford Classification of IgA nephropathy MEST or MEST-C score (which is based on five histopathological indicators: mesangial hypercellularity [M], endocapillary hypercellularity [E], segmental glomerulosclerosis [S], tubular atrophy or interstitial fibrosis [T], and the presence of crescents [C])[28,29] of T2 or C2 (>50% tubule-interstitial fibrosis or the presence of crescents in >25% of glomeruli). Full eligibility criteria are provided in the protocol.

PROCEDURES

Sibeprenlimab was administered as a single 100-ml intravenous infusion (in 0.9% sodium chloride solution) over the course of 1 hour, followed by a 25-ml saline flush. Placebo consisted of equivalent volumes of saline. To maintain blinding among the trial and clinical staff and the patients, a site designee who was aware of the trial-group assignments prepared the infusions. Doses were administered monthly; patients were to receive a total of 12 doses.

END POINTS AND ASSESSMENTS

The primary efficacy end point was the change from baseline in the 24-hour urinary protein-to-creatinine ratio (measured on the natural log scale and derived from a 24-hour urine collection) at month 12. Patients performed 24-hour urine collections at screening and at months 9, 12, and 16. In addition, an untimed urine sample was obtained at each monthly infusion visit to measure the spot urinary protein-to-creatinine ratio.

Secondary end points included the change from baseline in the 24-hour urinary protein-to-creatinine ratio at months 9 and 16, clinical remission (defined as a decrease in the level of urinary protein excretion to <300 mg per day), the change from baseline in the eGFR at month 12, and pharmacodynamics (the change from baseline in the total serum IgG, IgA, and IgM levels at months 9, 12, and 16). Safety end points included adverse events, clinical laboratory assessments, and physical examination findings. Medical history and adverse events were documented according to the *Medical Dictionary for Regulatory Activities* (MedDRA), version 24.0. Exploratory end points included the change from baseline in the circulating lymphocyte count, in the level of free APRIL, and in the level of galactose-deficient IgA1.

Data regarding race, ethnic group, age, sex, and gender identity were obtained at baseline, as reported by the patient. Patients were assessed at baseline; on days 8, 18, and 30; and then monthly through month 14. The end-of-trial visit for the final assessments of safety, efficacy, and pharmacodynamics occurred at month 16.

STATISTICAL ANALYSIS

The sample size was based on the assumption that there would be a linear dose response in the reduction of urinary protein-to-creatinine ratio of 0% reduction in the placebo group, 15% in the sibeprenlimab 2-mg group, 30% in the sibeprenlimab 4-mg group, and 45% in the sibeprenlimab 8-mg group. To test the linear dose response, the linear contrast statement of −3, −1, 1, and 3 was evaluated for the placebo group, the sibeprenlimab 2-mg group, the sibeprenlimab 4-mg group, and the sibeprenlimab 8-mg group, respectively, and analysis of the urinary protein-to-creatinine ratio on the natural log scale generated an expected mean change from baseline of 0, −0.163, −0.357, and −0.593, respectively. In addition, the pairwise comparisons of each of the sibeprenlimab dose levels with placebo were tested. With the use of an analysis-of-variance model with a standard deviation of 0.87[30] and on the basis of assumptions of 80% power to detect a difference between the sibeprenlimab groups and the placebo group, a two-sided type I error rate of 0.05, and a dropout rate of approximately

20%, the required sample size was determined to be 36 patients per group, or 144 patients overall.

Efficacy was evaluated in the modified intention-to-treat population, which included all the patients who had undergone randomization and had received at least one complete dose of sibeprenlimab or placebo. Safety was assessed in the safety population, which included all the patients who had undergone randomization and had received any amount of sibeprenlimab or placebo. Patients were included in the pharmacodynamic analysis if they had had a baseline measure and at least one measure after the start of administration of sibeprenlimab or placebo that could be evaluated.

The primary efficacy end point, the change from baseline in the log-transformed 24-hour urinary protein-to-creatinine ratio at month 12, was calculated as follows: $\log(t_i) - \log(t_0) = \log(t_i/t_0)$, where t_i is the value at any time point after baseline and t_0 is the baseline value. Log transformation and derivation of the urinary protein-to-creatinine ratio from a 24-hour urine collection were used to normalize the data, given that such data are typically skewed. Formal statistical hypothesis testing of the linear trend of dose response was performed on the primary end point at a two-sided, 0.048 significance level to preserve the trialwide, two-sided type I error rate at 0.05, while accounting for a planned interim efficacy analysis (see the statistical analysis plan, provided with the protocol). A regression model for repeated measures was used, with trial-group assignment, visit, randomization strata, and the interaction between visit and trial-group assignment as class effects and the baseline urinary protein-to-creatinine ratio on the natural log scale as a fixed-effect covariate.

For the secondary efficacy end points, including the change from baseline in the eGFR at month 12, the regression model for repeated measures was fitted to evaluate the effect of sibeprenlimab, with trial-group assignment, visit, randomization strata, and the interaction between visit and trial-group assignment as class effects and baseline eGFR as a covariate. The annualized slope of the regression line for eGFR, estimated over a period of 12 months, was fitted by means of a linear mixed-effects model with random effects, with trial-group assignment, time (as a continuous variable), the interaction between time and trial-group assignment, randomization strata, and baseline eGFR as fixed effects and the intercept and time slope as random effects.

The unstructured covariance matrix was used in both regression models for repeated measures for the change from baseline in the 24-hour urinary protein-to-creatinine ratio and the change from baseline in the eGFR, as well as in the linear mixed-effects model with random effects for the annualized slope of the eGFR. Within the regression models, missing data were assumed to be missing at random.

Formal statistical hypothesis testing was performed only on the primary end point. There were no multiplicity adjustments for the analyses of other efficacy end points; data are reported with 95% confidence intervals, which should not be interpreted as hypothesis tests. Statistical analyses were performed with the use of SAS software, version 9.4.

RESULTS

PATIENT CHARACTERISTICS

The trial was conducted from June 2020 through May 2023. A total of 155 patients were enrolled and underwent randomization. Patients were randomly assigned to receive sibeprenlimab at a dose of 2 mg per kilogram (38 patients), 4 mg per kilogram (41 patients), or 8 mg per kilogram (38 patients) or placebo (38 patients). The median duration of follow-up was 16.0 months. The demographic and clinical characteristics of the patients were generally similar among the four groups at baseline (Table 1). The placebo group was slightly younger, had a greater proportion of women, had a higher median baseline eGFR, and had more severe proteinuria (as evidenced by a higher median level of urinary protein excretion per day) than the sibeprenlimab groups. Details of the kidney biopsy findings are provided in Table S1 in the Supplementary Appendix. The placebo group had a higher mean percentage of crescents and a longer time since biopsy than the sibeprenlimab groups. The trial population was generally representative of the overall population of patients with IgA nephropathy (Table S2).

The full treatment course (12 doses) was completed by 146 of the 155 patients (94.2%) (Fig. S1). Among the 155 patients, the mean adherence to sibeprenlimab or placebo was 95.1%; the mean number of doses received was 11.4 per patient.

Table 1. Demographic and Clinical Characteristics at Baseline.*

Characteristic	Sibeprenlimab, 2 mg/kg (N=38)	Sibeprenlimab, 4 mg/kg (N=41)	Sibeprenlimab, 8 mg/kg (N=38)	Pooled Sibeprenlimab Groups (N=117)	Placebo (N=38)	Overall (N=155)
Median age (range) — yr	41 (25–71)	39 (20–73)	42 (23–72)	40 (20–73)	36 (18–52)	39 (18–73)
Sex — no. (%)						
Female	16 (42.1)	15 (36.6)	12 (31.6)	43 (36.8)	24 (63.2)	67 (43.2)
Male	22 (57.9)	26 (63.4)	26 (68.4)	74 (63.2)	14 (36.8)	88 (56.8)
Race or ethnic group — no. (%)†						
American Indian or Alaska Native	0	0	1 (2.6)	1 (0.9)	0	1 (0.6)
Asian	28 (73.7)	31 (75.6)	28 (73.7)	87 (74.4)	28 (73.7)	115 (74.2)
Black	0	1 (2.4)	0	1 (0.9)	0	1 (0.6)
White	9 (23.7)	9 (22.0)	8 (21.1)	26 (22.2)	10 (26.3)	36 (23.2)
Other	1 (2.6)	0	1 (2.6)	2 (1.7)	0	2 (1.3)
Geographic region — no. (%)‡						
Japan	5 (13.2)	5 (12.2)	5 (13.2)	15 (12.8)	4 (10.5)	19 (12.3)
Rest of world	33 (86.8)	36 (87.8)	33 (86.8)	102 (87.2)	34 (89.5)	136 (87.7)
Body-mass index — mean±SD§	27.2±4.5	28.1±6.4	27.6±5.8	27.6±5.6	27.4±6.7	27.6±5.9
History of hypertension — no. (%)	29 (76.3)	31 (75.6)	28 (73.7)	88 (75.2)	24 (63.2)	112 (72.3)
Median time since diagnostic kidney biopsy — days	781.0	288.0	364.0	490.0	933.0	565.0
Receiving ACE inhibitor or ARB therapy — no. (%)¶	37 (97.4)	40 (97.6)	37 (97.4)	114 (97.4)	38 (100.0)	152 (98.1)
SGLT2 inhibitor use at baseline — no. (%)‖	3 (7.9)	2 (4.9)	1 (2.6)	6 (5.1)	3 (7.9)	9 (5.8)
Median baseline urinary protein excretion (range) — g per day	1.47 (0.67–6.92)	1.93 (0.33–8.60)	1.90 (0.76–12.44)	1.78 (0.33–12.44)	2.13 (0.76–8.48)	—
Geometric mean baseline 24-hr urinary protein-to-creatinine ratio (GSE) — g of protein/g of creatinine	1.46 (0.12)	1.53 (0.12)	1.44 (0.14)	1.48 (0.07)	1.68 (0.17)	—
Baseline urinary protein-to-creatinine ratio — no. (%)						
≤2.0 g of protein/g of creatinine	24 (63.2)	26 (63.4)	24 (63.2)	74 (63.2)	25 (65.8)	99 (63.9)
>2.0 g of protein/g of creatinine	9 (23.7)	10 (24.4)	9 (23.7)	28 (23.9)	9 (23.7)	37 (23.9)
Data missing	5 (13.2)	5 (12.2)	5 (13.2)	15 (12.8)	4 (10.5)	19 (12.3)

Previous use of systemic immunosuppressive therapy — no. (%)	14 (36.8)	7 (17.1)	8 (21.1)	29 (24.8)	7 (18.4)	36 (23.2)
Median baseline eGFR (range) — ml/min/1.73 m²**	58.0 (35.0–154.0)	64.0 (35.0–133.0)	56.0 (34.0–109.0)	58.0 (34.0–154.0)	68.5 (33.0–116.0)	—

* This analysis included all the patients who had undergone randomization. Percentages may not total 100 because of rounding. GSE denotes geometric standard error.
† Race and ethnic group were reported by the patient.
‡ Randomization was stratified according to geographic region (Japan or the rest of the world).
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.
¶ Patients were receiving the highest dose of treatment with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin-receptor blocker (ARB) that was associated with minimal unacceptable side effects.
‖ This variable refers to the use of a sodium–glucose cotransporter 2 (SGLT2) inhibitor at least 3 months before screening. SGLT2 inhibitors were not approved at the time that this trial was designed; therefore, SGLT2 inhibitor use was not included in any enrollment criteria.
** For the estimated glomerular filtration rate (eGFR), a one-way analysis-of-variance test did not show a significant difference among the trial groups (P=0.18).

Figure 1. Change from Baseline over Time in the 24-Hour Urinary Protein-to-Creatinine Ratio.

This analysis was performed with the use of a mixed model for repeated measures in the modified intention-to-treat population. The mean percent change is calculated as (1 − exponentiated least-squares mean) × 100%. I bars indicate standard errors.

PROTEINURIA

After 12 months of treatment, there was a significant linear treatment effect in the change from baseline in the 24-hour urinary protein-to-creatinine ratio (the primary end point) (P<0.001). The geometric mean ratio reduction (±SE) in the 24-hour urinary protein-to-creatinine ratio from baseline to month 12 was 47.2±8.2% in the sibeprenlimab 2-mg group, 58.8±6.1% in the sibeprenlimab 4-mg group, 62.0±5.7% in the sibeprenlimab 8-mg group, and 20.0±12.6% in the placebo group (Fig. 1 and Table 2), showing a dose-dependent effect of sibeprenlimab on proteinuria. The mean percent change in the spot urinary protein-to-creatinine ratio over time is provided in Figure S2. The reductions in the urinary protein-to-creatinine ratio that were seen at month 9 were maintained through month 16 in the sibeprenlimab 4-mg and 8-mg groups but began returning toward baseline by month 16 in the 2-mg group (Fig. 1).

The percentage of patients who had clinical remission at month 12 was 7.9% (3 of 38 patients), 12.2% (5 of 41 patients), 26.3% (10 of 38 patients), and 2.6% (1 of 38 patients) in the sibeprenlimab 2-mg, 4-mg, and 8-mg groups and the placebo group, respectively. The percentage of patients whose urinary protein excretion level decreased

Table 2. Primary End Point and Select Secondary and Exploratory End Points.*

End Point	Sibeprenlimab, 2 mg/kg (N=38)	Sibeprenlimab, 4 mg/kg (N=41)	Sibeprenlimab, 8 mg/kg (N=38)	Placebo (N=38)
Geometric mean ratio reduction from baseline in 24-hr urinary protein-to-creatinine ratio — %†				
Month 9	49.6±7.7	56.7±6.2	62.8±5.5	12.7±13.4
Month 12, primary end point	47.2±8.2	58.8±6.1	62.0±5.7	20.0±12.6
Month 16	36.5±10.6	58.0±6.6	64.6±5.7	10.6±15.0
Geometric mean urinary protein-to-creatinine ratio reduction at month 12 relative to placebo — % (95% CI)‡	33.96±13.7 (0.4 to 56.2)	48.45±10.4 (23.2 to 65.4)	52.52±9.7 (28.8 to 68.4)	—
Geometric mean ratio change from baseline to month 12 in urinary protein-to-creatinine ratio (95% CI)				
≤2.0 g of protein/g of creatinine at baseline	0.7 (0.5 to 0.9)	0.4 (0.2 to 0.7)	0.4 (0.3 to 0.6)	1.0 (0.7 to 1.4)
>2.0 g of protein/g of creatinine at baseline	0.5 (0.3 to 0.8)	0.6 (0.3 to 1.0)	0.5 (0.3 to 0.8)	0.8 (0.6 to 1.1)
Least-squares mean change from baseline in urinary protein excretion at month 12 — g per day§	−0.68±0.2	−0.86±0.2	−1.06±0.2	−0.21±0.2
Least-squares mean change from baseline in eGFR at month 12 — ml/min/1.73 m^2§	−2.7±1.8	0.2±1.7	−1.5±1.8	−7.4±1.8
Least-squares mean difference in eGFR relative to placebo from baseline to month 12 (95% CI) — ml/min/1.73 m^2	4.6 (−0.3 to 9.5)	7.6 (2.8 to 12.3)	5.8 (0.9 to 10.7)	—
Annualized eGFR slope estimate from baseline to month 12 — ml/min/1.73 m^2¶	−4.1±1.7	0.1±1.6	−0.8±1.6	−5.9±1.7
Treatment difference in eGFR slope relative to placebo (95% CI) — ml/min/1.73 m^2	1.81 (−2.8 to 6.4)	5.96 (1.5 to 10.4)	5.08 (0.5 to 9.6)	—

* Plus–minus values are geometric or least-squares means ±SE. All the analyses were performed in the modified intention-to-treat population. CI denotes confidence interval.
† The geometric mean ratio reduction was calculated as (1−exponentiated least-squares mean) × 100%, and the corresponding SE was calculated as (exponentiated least-squares mean) × (SE of least-squares mean) × 100%.
‡ The difference in the geometric mean ratio reduction was calculated as (1−exponentiated least-squares mean difference) × 100%, and the corresponding SE was calculated as (exponentiated least-squares mean difference) × (SE of least-squares mean difference) × 100%.
§ A regression model for repeated measures was used for this analysis.
¶ A linear mixed-effects model was used for this analysis.

to less than 500 mg per day at month 12 was 13.2% (5 of 38 patients), 29.3% (12 of 41 patients), 28.9% (11 of 38 patients), and 2.6% (1 of 38 patients), respectively, and the percentage of patients whose level decreased to less than 1 g per day at month 12 was 42.1% (16 of 38 patients), 41.5% (17 of 41 patients), 55.3% (21 of 38 patients), and 18.4% (7 of 38 patients), respectively. Data regarding the absolute change in the urinary protein excretion level are presented in Table 2. Across the four trial groups, the mean baseline arterial blood pressure ranged from 95.9 to 96.7 mm Hg and did not differ appreciably over time (Table S3).

ESTIMATED GLOMERULAR FILTRATION RATE

The least-squares mean (±SE) changes from baseline in eGFR at the end of the 12-month treatment period were −2.7±1.8, 0.2±1.7, and −1.5±1.8 ml per minute per 1.73 m^2 in the sibeprenlimab 2-mg, 4-mg, and 8-mg groups, respectively, as compared with −7.4±1.8 ml per minute per 1.73 m^2 in the placebo group (Table 2). The least-squares mean difference in eGFR relative to placebo from baseline to month 12 was 7.6 ml per minute per 1.73 m^2 (95% confidence interval [CI], 2.8 to 12.3) in the sibeprenlimab 4-mg group and 5.8 ml per minute per 1.73 m^2 (95% CI, 0.9 to 10.7) in the sibeprenlimab 8-mg group. The annualized eGFR

slope estimate was attenuated in all three sibeprenlimab groups as compared with placebo (Table 2). Throughout the first 3 months of the trial, the median eGFR in the pooled sibeprenlimab groups was stable, at 58.0 ml per minute per 1.73 m^2 (range, 34.0 to 154.0), 59.0 ml per minute per 1.73 m^2 (range, 34.0 to 148.0), 61.0 ml per minute per 1.73 m^2 (range, 31.0 to 143.0), and 61.0 ml per minute per 1.73 m^2 (range, 31.0 to 146.0), respectively, at baseline and on days 30, 60, and 90. In the placebo group, the median eGFR was 68.5 ml per minute per 1.73 m^2 (range, 33.0 to 116.0), 63.5 ml per minute per 1.73 m^2 (range, 32.0 to 116.0), 67.5 ml per minute per 1.73 m^2 (range, 28.0 to 119.0), and 62.0 ml per minute per 1.73 m^2 (range, 32.0 to 119.0), respectively, at baseline and on days 30, 60, and 90.

LYMPHOCYTE COUNT

The mean lymphocyte count showed no appreciable change from baseline at month 12. Results over time are provided in Table S4.

SAFETY

The incidence of adverse events that occurred after the start of administration of sibeprenlimab or placebo was similar in the sibeprenlimab and placebo groups (Table 3). The most common adverse events (incidence of ≥5% in the pooled sibeprenlimab group) were coronavirus disease 2019 (Covid-19), pyrexia, nasopharyngitis, upper respiratory tract infection, headache, hypertension, diarrhea, and muscle spasm. No increased risk of infection (MedDRA system organ class, infections and infestations) was observed with sibeprenlimab (49.6%) as compared with placebo (55.3%). The incidence of Covid-19 was higher in the placebo group than in any of the sibeprenlimab groups. A majority of the adverse events were mild or moderate in severity.

The incidence of serious adverse events (none of which were considered by the investigators to be related to sibeprenlimab or placebo) was equally distributed across the sibeprenlimab and placebo groups (Table 3 and Table S5). One death, due to respiratory failure in a patient with underlying chronic obstructive pulmonary disease, was reported in the placebo group.

PHARMACODYNAMICS

In the sibeprenlimab 4-mg and 8-mg groups, the mean levels of serum galactose-deficient IgA1 and IgA were reduced by approximately 65%, IgG by approximately 35%, and IgM by approximately 75%; smaller reductions were observed in the sibeprenlimab 2-mg group (Fig. 2A and Fig. S3). The magnitude of the reduction in the mean galactose-deficient IgA1 level at month 12 relative to the reduction in the mean IgA level is shown in Figure 2B. Recovery of the mean galactose-deficient IgA1, IgA, IgG, and IgM levels, with dose-dependent pharmacokinetics, was seen after discontinuation of sibeprenlimab (after month 12).

Treatment with sibeprenlimab suppressed the serum level of APRIL in a dose-dependent manner, with near-complete and sustained suppression in the sibeprenlimab 4-mg and 8-mg groups. The mean APRIL levels returned to baseline, with dose-dependent pharmacokinetics, after cessation of sibeprenlimab (Fig. 2C).

DISCUSSION

The existing literature indicates that APRIL and galactose-deficient IgA1 play a pivotal role in the pathogenesis of IgA nephropathy.[8-10,16-22,31] The results of the current trial showed robust suppression of serum APRIL levels and of galactose-deficient IgA1 levels after administration of intravenous sibeprenlimab. These changes led to significantly greater reductions in proteinuria and greater stabilization of eGFR decline with sibeprenlimab than with placebo, particularly with the higher doses (4 mg per kilogram and 8 mg per kilogram).

At the end of the 12-month treatment period, the sibeprenlimab 4-mg and 8-mg groups showed a greater reduction in the log-adjusted urinary protein-to-creatinine ratio (48% and 53%, respectively) as compared with placebo, and this reduction was sustained through month 16 (5 months after the last dose). Furthermore, 12.2% of the patients in the sibeprenlimab 4-mg group and 26.3% of those in the sibeprenlimab 8-mg group had a reduction in the urinary protein excretion level to less than 300 mg per day at month 12; in the placebo group, only 2.6% of the patients had such a reduction. The reduction in proteinuria was similar in subgroups stratified according to the baseline 24-hour urinary protein-to-creatinine ratio (≤2.0 vs. >2.0 g of protein per gram of creatinine).

As compared with placebo, patients in the sibeprenlimab 4-mg and 8-mg groups had a beneficial change in the eGFR. This reflects a stabilization

Table 3. Adverse Events.*

Event	Sibeprenlimab, 2 mg/kg (N=38)	Sibeprenlimab, 4 mg/kg (N=41)	Sibeprenlimab, 8 mg/kg (N=38)	Pooled Sibeprenlimab Groups (N=117)	Placebo (N=38)
	number of patients (percent)				
Any adverse event	28 (73.7)	33 (80.5)	31 (81.6)	92 (78.6)	27 (71.1)
Maximum severity of any adverse event					
Mild	19 (50.0)	22 (53.7)	22 (57.9)	63 (53.8)	23 (60.5)
Moderate	7 (18.4)	9 (22.0)	8 (21.1)	24 (20.5)	3 (7.9)
Severe	2 (5.3)	2 (4.9)	1 (2.6)	5 (4.3)	1 (2.6)
Adverse events related to sibeprenlimab or placebo	7 (18.4)	7 (17.1)	4 (10.5)	18 (15.4)	5 (13.2)
Serious adverse events	2 (5.3)	2 (4.9)	1 (2.6)	5 (4.3)	2 (5.3)
Adverse events that led to interruption of sibeprenlimab or placebo	5 (13.2)	1 (2.4)	3 (7.9)	9 (7.7)	0
Adverse events that led to discontinuation of sibeprenlimab or placebo	1 (2.6)	0	0	1 (0.9)	0
Adverse events that resulted in death	0	0	0	0	1 (2.6)
Adverse events with an incidence of ≥5% in the pooled sibeprenlimab group					
Covid-19	11 (28.9)	11 (26.8)	13 (34.2)	35 (29.9)	16 (42.1)
Pyrexia	5 (13.2)	5 (12.2)	6 (15.8)	16 (13.7)	6 (15.8)
Nasopharyngitis	4 (10.5)	5 (12.2)	6 (15.8)	15 (12.8)	3 (7.9)
Upper respiratory tract infection	3 (7.9)	5 (12.2)	2 (5.3)	10 (8.5)	0
Headache	1 (2.6)	5 (12.2)	3 (7.9)	9 (7.7)	4 (10.5)
Hypertension	4 (10.5)	3 (7.3)	0	7 (6.0)	1 (2.6)
Diarrhea	0	4 (9.8)	2 (5.3)	6 (5.1)	1 (2.6)
Muscle spasm	1 (2.6)	4 (9.8)	1 (2.6)	6 (5.1)	1 (2.6)
Adverse events of special interest					
Adverse events related to infections and infestations system organ class	15 (39.5)	23 (56.1)	20 (52.6)	58 (49.6)	21 (55.3)

* Shown are adverse events that occurred after the start of administration of sibeprenlimab or placebo. This analysis was performed in all the patients who had undergone randomization and had received any amount of sibeprenlimab or placebo. Covid-19 denotes coronavirus disease 2019.

of the eGFR with sibeprenlimab as compared with the secular eGFR decline observed with placebo. A recent long-term cohort study showed that almost all the patients with IgA nephropathy were at risk for progression to kidney failure within their expected lifetime unless a rate of eGFR loss of 1 ml per minute per 1.73 m^2 per year or lower was maintained.[32] Currently, other available therapies for IgA nephropathy have not shown a sustained effect of this magnitude on eGFR stabilization, thus emphasizing the need for new and more effective treatment options.

Patients were followed for approximately 5 months after administration of the final dose of sibeprenlimab or placebo. During this period, there was a return toward the baseline levels of total serum IgA and galactose-deficient IgA1 in the sibeprenlimab groups, with dose-dependent pharmacokinetics. The substantial reductions in the mean urinary protein-to-creatinine ratio that were observed in the sibeprenlimab 4-mg and 8-mg groups were maintained through month 16; by contrast, the mean urinary protein-to-creatinine ratio in the sibeprenlimab 2-mg group started to return toward the baseline level during this time. These observations suggest that sustained sup-

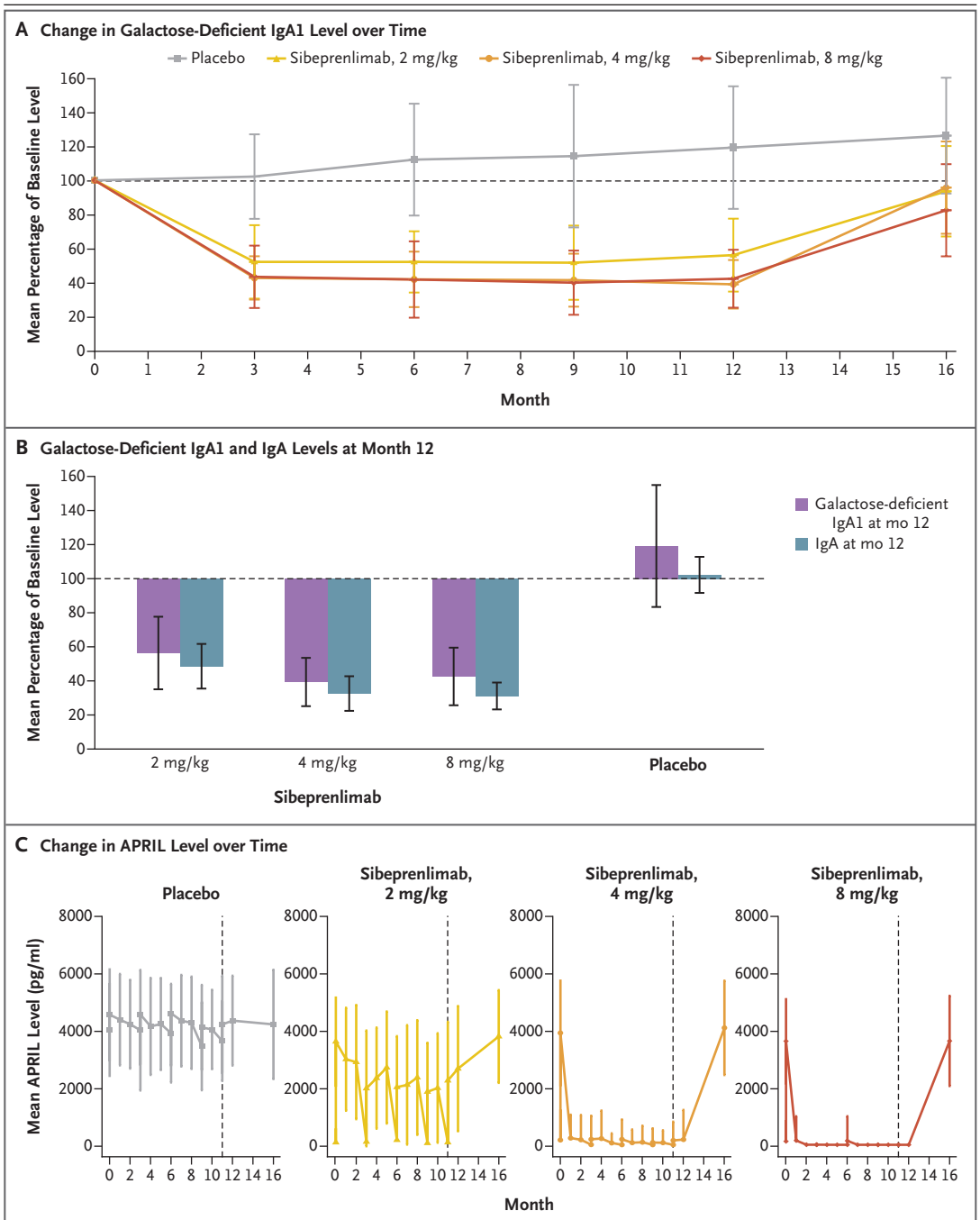

Figure 2. Change in the Galactose-Deficient IgA1 Level over Time, Galactose-Deficient IgA1 and IgA Levels at Month 12, and Change in the APRIL Level over Time.

I bars indicate standard deviations. The vertical dashed lines in Panel C represent the last dose of sibeprenlimab. APRIL denotes a proliferation-inducing ligand.

pression of APRIL may be needed to maintain clinical efficacy, given that APRIL and galactose-deficient IgA1 suppression were not sustained after discontinuation of sibeprenlimab.

The safety profile of sibeprenlimab showed no evidence of adverse toxic effects or clinically meaningful immunosuppression through month 16. The incidence of adverse events that occurred

after the start of administration of sibeprenlimab or placebo was similar in the pooled sibeprenlimab group and the placebo group. Despite reductions in the serum levels of IgA, IgG, and IgM in the sibeprenlimab groups, there was no increase in the incidence of infections with sibeprenlimab, and moreover, Covid-19 occurred more frequently in the placebo group than in any sibeprenlimab group. The results of the initial clinical sibeprenlimab trial[26] showed that sibeprenlimab selectively inhibited APRIL and did not affect the level of B-cell activating factor of the tumor necrosis factor α family (BAFF), thus avoiding lymphocyte depletion and its potential consequences, which have been associated with dual inhibition of APRIL and BAFF.[33]

In the current trial, we speculate that the magnitude of observed baseline differences in the percentage of crescents and the time since biopsy is unlikely to affect the efficacy results and conclusions. A strength of our trial is the racial and demographic composition, which is consistent with the known distribution of IgA nephropathy[34] and thus supports the generalizability of the results. However, phase 2 data should be interpreted judiciously. The efficacy and safety of sibeprenlimab in a larger population of patients with IgA nephropathy are under investigation in an ongoing phase 3 trial (ClinicalTrials.gov number, NCT05248646). In the current trial, 12 months of treatment with sibeprenlimab resulted in a significantly greater decrease in proteinuria than placebo in patients with IgA nephropathy.

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