ORIGINAL ARTICLE

Interim Analysis of a Phase 3 Trial of Povetacicept in IgA Nephropathy

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ABSTRACT

BACKGROUND

B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) have distinct roles in IgA-producing B-cell populations and appear to be central to the pathogenesis of IgA nephropathy. Povetacicept, an enhanced, variant transmembrane activator and calcium-modulator and cyclophilin-ligand interactor (TACI)–Fc fragment fusion therapeutic, is engineered for dual inhibition of BAFF and APRIL.

METHODS

In this ongoing, phase 3, double-blind, placebo-controlled trial, participants with biopsy-proven IgA nephropathy receiving stable background therapy were randomly assigned in a 2:1 ratio to receive povetacicept at a dose of 80 mg or placebo subcutaneously every 4 weeks. The primary end point of this prespecified interim analysis was the change in the 24-hour urinary protein-to-creatinine ratio at week 36. Secondary end points were the change at week 36 in galactose-deficient IgA1 levels and hematuria resolution at week 36 among participants with baseline hematuria.

RESULTS

A total of 557 participants received povetacicept (372 participants) or placebo (185 participants). Efficacy analyses included the first 199 participants who had undergone randomization (131 in the povetacicept group and 68 in the placebo group). The 24-hour urinary protein-to-creatinine ratio decreased by 52.0% with povetacicept and by 4.3% with placebo by week 36 (adjusted difference, −49.8 percentage points; 95% confidence interval [CI], −58.6 to −39.2; P<0.001). Galactose-deficient IgA1 levels decreased by 77.4% with povetacicept and increased by 9.1% with placebo (adjusted difference, −79.3 percentage points; 95% CI, −82.2 to −75.9; P<0.001). Among the participants with baseline hematuria, resolution occurred in 85% with povetacicept and in 23% with placebo (adjusted difference, 62 percentage points; 95% CI, 45 to 78; P<0.001). The incidence of adverse events (75% with povetacicept and 78% with placebo) and serious adverse events (3% and 4%, respectively) were similar in the trial groups.

CONCLUSIONS

Povetacicept led to a significantly greater reduction in the 24-hour urinary protein-to-creatinine ratio than placebo by week 36 in participants with IgA nephropathy. (Funded by Vertex Pharmaceuticals; RAINIER AIS-D08 ClinicalTrials.gov number, NCT06564142.)

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*A complete list of the investigators in the RAINIER AIS-D08 trial group is provided in the Supplementary Appendix, available at NEJM.org.

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IgA nephropathy, the most common primary glomerular disease, is associated with a progressive decrease in the estimated glomerular filtration rate (eGFR), which leads to a substantial lifetime risk of kidney failure.[1-5] Despite supportive therapies such as sodium–glucose cotransporter 2 (SGLT2) inhibitors, many patients remain at risk for disease progression.[6] The pathogenesis of IgA nephropathy involves the formation of galactose-deficient IgA1 immune complexes that deposit in the glomerular mesangium, with consequent inflammation that leads to proteinuria, hematuria, and progressive kidney injury.[7,8] Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines recommend a dual approach to management: targeted therapies to prevent IgA immune-complex formation and kidney injury and agents to attenuate the maladaptive response to nephron loss.[9] Proteinuria, hematuria, and elevated levels of galactose-deficient IgA1 are strong predictors of kidney-function decline, whereas reductions of these predict stabilization or preservation of kidney function. Moreover, a reduction in proteinuria is a commonly used, validated surrogate end point for assessing the efficacy of therapies in IgA nephropathy.[6,9,10]

Levels of B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) are typically elevated in patients with IgA nephropathy. In addition, these two cytokines of the tumor necrosis factor superfamily regulate B-cell maturation and plasmablast survival and together cause activation, differentiation, and proliferation of the IgA-producing B-cell populations central to the pathogenesis of IgA nephropathy.[11,12] Both cytokines act through partially overlapping receptors and support distinct B-cell subpopulations — BAFF acts predominantly through BAFF receptors on germinal-center B cells, whereas APRIL drives IgA isotype class switching and supports the survival of plasmablasts and long-lived plasma cells through transmembrane activator and calcium-modulator and cyclophilin-ligand interactor (TACI) and B-cell maturation antigen.[13,14] Povetacicept was engineered with a TACI domain that confers a greater binding affinity to BAFF and APRIL than wild-type TACI, with evidence of increased potency, improved pharmacokinetics, and broader tissue distribution.[15,16]

In a phase 1–2, open-label study (RUBY-3), povetacicept at a dose of 80 mg every 4 weeks led to sustained reductions in disease-activity measures among 21 adults with IgA nephropathy receiving stable background therapy — 24-hour urinary protein-to-creatinine ratio at week 48 was reduced by 64%, along with reductions in galactose-deficient IgA1 levels, resolution of hematuria, and stabilization of eGFR.[17] In the phase 3 RAINIER AIS-D08 trial, we evaluated the efficacy and safety of povetacicept in adults with biopsy-confirmed IgA nephropathy at risk for disease progression and receiving stable background therapy. Here we report the prespecified interim analysis of this multicenter trial.



A Quick Take is available at NEJM.org



METHODS

TRIAL DESIGN AND PARTICIPANTS

Our trial is an ongoing, phase 3, double-blind, randomized, placebo-controlled, 2-year trial of the efficacy and safety of povetacicept in participants with IgA nephropathy receiving medication to lower proteinuria as stable background therapy (with proteinuria assessed as the 24-hour urinary protein-to-creatinine ratio); the trial is being conducted at 224 sites across 29 countries (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial enrolled a main cohort (557 participants) and an exploratory cohort (48 participants); the latter included participants with an eGFR of 20 to 29 ml per minute per 1.73 m^2 of body-surface area. Only the main cohort is discussed here.

Participants were randomly assigned in a 2:1 ratio to receive povetacicept at a dose of 80 mg or placebo subcutaneously every 4 weeks through week 100. Randomization was stratified according to 24-hour urinary protein-to-creatinine ratio (≤1.5 vs. >1.5, with protein and creatinine both measured in grams), as a measure of proteinuria; eGFR (30 to <60 vs. ≥60 ml per minute per 1.73 m^2); and geographic region (Japan vs. other Asia–Pacific vs. the rest of the world).

Adults with biopsy-proven IgA nephropathy, 24-hour urinary protein excretion of at least 1 g per day or 24-hour urinary protein-to-creatinine ratio of at least 0.75, and an eGFR of at least 30 ml per min per 1.73 m^2 were eligible. Participants were required to have received a stable and maximum tolerated dose of angiotensin-converting enzyme inhibitor or angiotensin II–receptor blocker for at least 12 weeks before screening. Use of other medications that lower

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proteinuria (e.g., an SGLT2 inhibitor) was allowed. Complete eligibility criteria are provided in the Supplementary Appendix.

TRIAL OVERSIGHT

The trial was designed by Vertex Pharmaceuticals in collaboration with the trial steering committee. An independent data monitoring committee provided safety oversight. Before enrollment, the trial was approved by the institutional review board or ethics committee at each site or region, and participants provided written informed consent. Data collection and analyses were performed by Vertex Pharmaceuticals and the trial investigators. The authors had access to complete aggregate trial data after the database lock, reviewed the manuscript, and approved the submission of the manuscript for publication. The trial investigators vouch for the accuracy and completeness of the data generated at their respective sites. The last author and all the authors employed by Vertex Pharmaceuticals had access to participant-level trial data; these authors vouch for the accuracy and completeness of all the data and for the fidelity of the trial to the protocol (available at NEJM.org). See the Supplementary Appendix for additional information.

END POINTS

The primary end point for this interim analysis was the change in the 24-hour urinary protein-to-creatinine ratio from baseline to week 36. The secondary end points for the interim analysis were the change in galactose-deficient IgA1 levels from baseline to week 36 and resolution of hematuria at week 36. Hematuria resolution was defined as a change from moderate-to-large amounts of blood in the urine at baseline, as assessed by a dipstick test, to a negative result or small amounts of blood on the dipstick test. Exploratory end points included the change in spot urinary protein-to-creatinine ratio, the change in 24-hour urinary protein excretion, the change in 24-hour urinary albumin-to-creatinine ratio, a 24-hour urinary protein-to-creatinine ratio of less than 0.5 or less than 0.3, the time to first resolution of hematuria, safety (adverse events that occurred during the treatment period), and the change in serum immunoglobulin levels.

STATISTICAL ANALYSIS

The change in the 24-hour urinary protein-to-creatinine ratio from baseline to week 36 was assessed on a natural log-transformed scale. We calculated that data from approximately 150 participants randomly assigned in a 2:1 ratio to receive povetacicept (100 participants) or placebo (50 participants) would provide more than 85% power to detect a 40% treatment difference in the change in the 24-hour urinary protein-to-creatinine ratio, assuming a common standard deviation of 0.75 (on a log-transformed scale)[18] and a two-sided significance level of 0.01.

The primary analysis population for the interim analysis included the first 199 participants who had undergone randomization and either had completed the week 36 visit or had discontinued the trial regimen early and had received their first dose at least 36 weeks before the data-cutoff date for the interim analysis. The change in the 24-hour urinary protein-to-creatinine ratio from baseline to week 36, assessed on a natural log scale, was analyzed with the use of a mixed-effects model for repeated measures (MMRM) with data up to week 36, regardless of initiation of rescue therapy for IgA nephropathy (or other therapies that could materially affect efficacy) or discontinuation of the trial regimen. Data that were missing after these events were imputed with control-based multiple imputations. Other missing data were imputed under the assumption that they were missing at random. The model included baseline eGFR and baseline 24-hour urinary protein-to-creatinine ratio (assessed on a natural log scale) as covariates and region (Asia–Pacific vs. the rest of the world), trial group, visit, and trial group–by–visit interaction as fixed effects.

The change in galactose-deficient IgA1 levels from baseline to week 36 (a secondary end point) was analyzed on the basis of an MMRM similar to the primary end point. For hematuria resolution at week 36 (a secondary end point), the P value was calculated with the Cochran–Mantel–Haenszel test.

The primary and secondary end points were controlled for multiplicity with the use of a hierarchical testing procedure with a two-sided alpha level of 0.01 at the interim analysis. Details regarding the analysis methods, handling of intercurrent events and missing data (Table S1), and multiplicity are available in the Supplementary Appendix.

For the exploratory end points, the widths of the reported 95% confidence intervals have not been adjusted for multiplicity and may not be

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used in place of hypothesis testing. Demographic and clinical characteristics at baseline and safety results are summarized descriptively.

RESULTS

POPULATION

The randomization and follow-up of the participants at the time of the interim analysis (January 16, 2026) is shown in Figure S2. Enrollment was completed in November 2025. A total of 557 participants underwent randomization (372 in the povetacicept group and 185 in the placebo group) and were included in the safety analyses. The first 199 participants who underwent randomization (131 in the povetacicept group and 68 in the placebo group) were included in the interim efficacy analyses (the primary analysis population for the interim analysis). In this population, 5 participants (4%) in the povetacicept group and 6 (9%) in the placebo group discontinued the trial regimen and 1 participant in each group discontinued the trial early.

Demographic and clinical characteristics were similar in the two trial groups in the primary analysis population for the interim analysis (Table 1 and Table S2) and in the overall trial population (Table S3) and were representative of the general population of persons with IgA nephropathy (Table S4). Of the 199 participants in the primary analysis population for the interim analysis, 118 (59%) were men and 122 (61%) were Asian; the mean age was 43.5 years. At baseline, the mean 24-hour urinary protein-to-creatinine ratio was 1.5 and the mean eGFR was 72.3 ml per minute per 1.73 m^2. A total of 99% of the participants (198 of 199) were receiving stable background medications, with 97% (194 of 199) receiving an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker and 66% (131 of 199) receiving an SGLT2 inhibitor. The mean time from initial renal biopsy to randomization was 4.4 years.

EFFICACY

Primary End Point

At week 36, the geometric mean percent reduction from baseline in the 24-hour urinary protein-to-creatinine ratio was 52.0% in the povetacicept group and 4.3% in the placebo group, which corresponds to an adjusted difference of −49.8 percentage points (95% confidence interval [CI], −58.6 to −39.2; P<0.001) (Fig. 1A). The proportion of participants with missing data for the primary end point was low (6 of 199 participants [3%]).

At week 4, the spot urinary protein-to-creatinine ratio (an exploratory end point) had decreased rapidly with povetacicept (geometric mean change, −15.0%) and had increased with placebo (geometric mean change, 3.2%), with a geometric mean difference of −17.6 percentage points (95% CI, −28.4 to −5.1). The spot urinary protein-to-creatinine ratio continued to decrease over time in the povetacicept group while remaining closer to the baseline value in the placebo group (Fig. 1B). Results for all exploratory end-point analyses assessing 24-hour urinary protein-to-creatinine ratio, 24-hour urinary protein excretion, and 24-hour urinary albumin-to-creatinine ratio over time were consistent with the results of the analysis of the spot urinary protein-to-creatinine ratio, with between-group differences observed by the first postbaseline time point (week 12) and sustained improvement through week 36 with povetacicept (Fig. S3).

Prespecified subgroup analyses of the primary end point showed a similar treatment effect of povetacicept on the change in the 24-hour urinary protein-to-creatinine ratio at week 36 across subgroups with respect to age, race, ethnic group, sex, baseline 24-hour urinary protein-to-creatinine ratio, baseline eGFR, and region (Asia–Pacific vs. the rest of the world) (Fig. 2). Ad hoc subgroup analyses of the primary end point also showed a similar treatment effect of povetacicept across subgroups with respect to baseline use of an SGLT2 inhibitor, hematuria at baseline, and region (North America vs. the rest of the world) (Fig. S4).

At week 36, a total of 54 of 128 participants (42%) in the povetacicept group and 4 of 65 participants (6%) in the placebo group had a 24-hour urinary protein-to-creatinine ratio of less than 0.5 (Fig. S5A). A total of 23 of 128 participants (18%) in the povetacicept group and 1 of 65 participants (2%) in the placebo group had a 24-hour urinary protein-to-creatinine ratio of less than 0.3 at week 36 (Fig. S5B).

Secondary End Points

Galactose-deficient IgA1 levels had decreased 56.5% with povetacicept and 4.7% with placebo at week 4. With respect to the secondary end point (change in galactose-deficient IgA1 levels at week 36), these levels had decreased by 77.4% with povetacicept and increased by 9.1% with placebo, which corresponded to an adjusted dif-

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ference of –79.3 percentage points (95% CI, –82.2 to –75.9; P<0.001) (Fig. 3A). The percentage of participants with missing data for this secondary end point was low (7 of 199 participants [4%]).

Among the participants with hematuria at baseline, resolution of hematuria was observed in 85% of the participants in the povetacicept group and in 23% of those in the placebo group at week 36, which corresponded to a difference of 62 percentage points (95% CI, 45 to 78; P<0.001) (Fig. 3B). The median time to first hematuria resolution was 13 weeks in the povetacicept group and could not be estimated in the placebo group (Fig. S6). The percentage of participants with missing data for this secondary end point was low (2 of 103 participants [2%]).

SAFETY

At this prespecified interim analysis, the mean duration of exposure to the trial regimen in the safety population (the 557 participants in the main cohort who underwent randomization and received at least one dose of povetacicept or placebo) was 33.7 weeks in the povetacicept group and 33.4 weeks in the placebo group. The incidence of adverse events was generally similar in the two groups: 75% with povetacicept (279 of 372 participants) and 78% with placebo (145 of 185 participants) (Table 2). Adverse events were mainly mild or moderate. One participant (<1%) in the povetacicept group and 4 (2%) in the placebo group discontinued the trial regimen owing to an adverse event.

Table 1. Baseline Demographic and Clinical Characteristics of the Participants in the Primary Analysis Population for the Interim Analysis.*

Characteristic	Povetacicept (N=131)	Placebo (N=68)
Age — yr	44.1±12.5	42.5±11.8
Sex — no. (%)		
Male	76 (58)	42 (62)
Female	55 (42)	26 (38)
Race — no. (%)†		
Asian	82 (63)	40 (59)
White	47 (36)	26 (38)
Other	2 (2)	2 (3)
Geographic region — no. (%)‡		
Asia–Pacific	76 (58)	41 (60)
Europe and the Middle East	31 (24)	17 (25)
North America	24 (18)	10 (15)
Time from initial renal biopsy to randomization — yr	4.2±4.2	4.9±4.4
24-hour urinary protein-to-creatinine ratio§		
Mean	1.5±0.9	1.6±1.4
Distribution — no. (%)		
≤1.5	82 (63)	43 (63)
>1.5	49 (37)	25 (37)
eGFR§		
Mean — ml/min/1.73 m^2	74.4±30.3	68.4±29.5
Distribution — no. (%)		
<60 ml/min/1.73 m^2	54 (41)	30 (44)
≥60 ml/min/1.73 m^2	77 (59)	38 (56)
Galactose-deficient IgA1 — ng/ml	6591.7±4682.1	6169.7±4589.0

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Table 1. (Continued.)

Characteristic	Povetacicept (N = 131)	Placebo (N = 68)
Hematuria — no. (%)		
None	31 (24)	15 (22)
Low	33 (25)	17 (25)
Moderate	42 (32)	20 (29)
High	25 (19)	16 (24)
Blood pressure — mm Hg§		
Systolic	122.8±12.9	123.9±11.4
Diastolic	77.9±8.9	80.4±7.4
Previous immunosuppression for IgA nephropathy — no. (%)¶	17 (13)	10 (15)
Medications that lower proteinuria — no. (%)‖		
Any	130 (99)	68 (100)
ACE inhibitor or ARB	127 (97)	67 (99)
SGLT2 inhibitor	88 (67)	43 (63)
Mineralocorticoid receptor antagonist	19 (15)	8 (12)
Any Endothelin A receptor antagonist	2 (2)	2 (3)

* Plus–minus values are means ±SD. The primary analysis population for the interim analysis comprised the first 199 participants who had undergone randomization and either had completed the week 36 visit or had discontinued the trial regimen early and had received their first dose at least 36 weeks before the data-cutoff date for the interim analysis. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, eGFR estimated glomerular filtration rate, and SGLT2 sodium–glucose cotransporter 2.

† Race was reported by the participants.

‡ Asia–Pacific includes Australia, China, Hong Kong, Japan, South Korea, and Taiwan. Europe and the Middle East includes Austria, Croatia, the Czech Republic, Denmark, Estonia, France, Germany, Hungary, Ireland, Israel, Italy, Latvia, Lithuania, the Netherlands, Norway, Poland, Spain, Sweden, Turkey, and the United Kingdom. North America includes the United States.

§ The baseline value was the mean of the two most recent samples obtained before administration of the first dose of povetacicept or placebo during the treatment period. For the 24-hour urinary protein-to-creatinine ratio, both protein and creatinine were measured in grams. The eGFR was calculated with the 2021 Chronic Kidney Disease Epidemiology Collaboration creatinine equation.

¶ Previous immunosuppression for IgA nephropathy was defined as a date of initiation of immunosuppression that occurred before the date of administration of the first dose of povetacicept or placebo, regardless of when immunosuppression ended.

‖ Medications that lower proteinuria included medication being taken on the first day of administration of povetacicept or placebo.

Serious adverse events occurred in 11 participants (3%) in the povetacicept group and in 8 (4%) in the placebo group. No serious adverse events were judged by the investigators as being related to povetacicept. No deaths were reported.

Injection-site reactions occurred in 54 participants (15%) receiving povetacicept and in 4 participants (2%) receiving placebo (Table 2). Injection-site reactions were mild in all the participants except for 1 participant who had a moderate injection-site reaction; none led to interruption or discontinuation of the trial regimen.

Infection occurred in 171 participants (46%) in the povetacicept group, as compared with 75 participants (41%) in the placebo group. Most infections were mild to moderate. Upper respiratory tract infection was the most common infection (in 89 participants [16%] overall). The incidence of serious or severe infection was the same in the two trial groups (2 participants [1%] in the povetacicept group and 1 [1%] in the placebo group), and none of these infections led to discontinuation of the trial regimen (Table S5). No opportunistic infections were reported.

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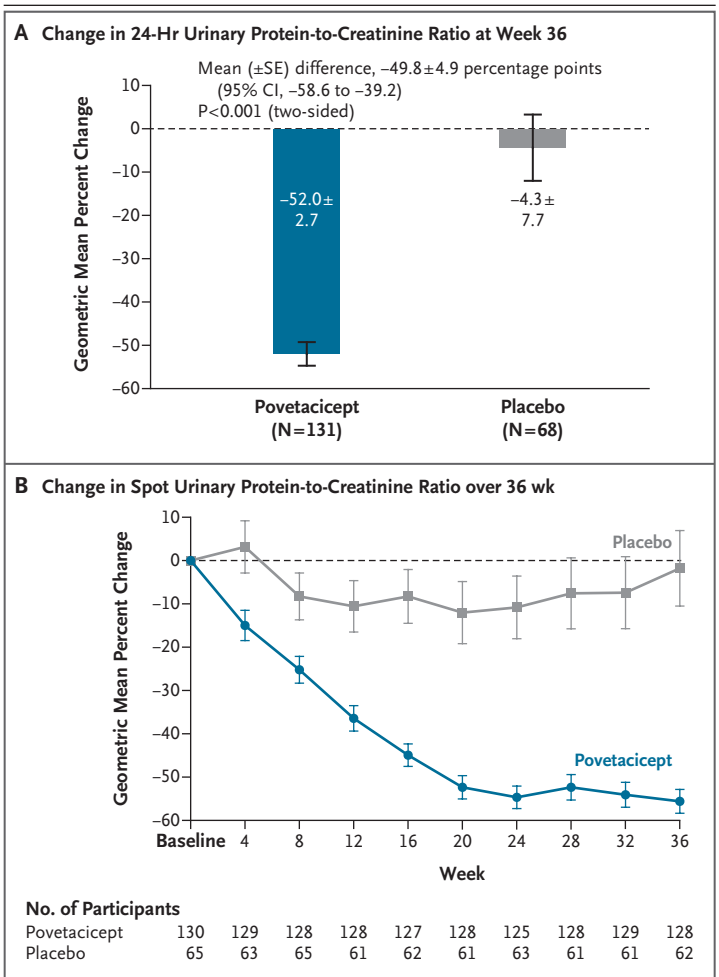

Figure 1. Percent Change in 24-Hour Urinary Protein-to-Creatinine Ratio (Primary End Point) and in Spot Urinary Protein-to-Creatinine Ratio.

Panel A shows the geometric mean percent change in the 24-hour urinary protein-to-creatinine ratio from baseline to week 36 (multiplicity-controlled primary end point) in the primary analysis population for the interim analysis. Panel B shows the geometric mean percent change in the spot urinary protein-to-creatinine ratio (an exploratory end point) from baseline to 36 weeks in the primary analysis population for the interim analysis. The primary analysis population for the interim analysis comprised the first 199 participants who had undergone randomization and either had completed the week 36 visit or had discontinued the trial regimen early and had received the first dose at least 36 weeks before the data-cutoff date for the interim analysis. For the 24-hour urinary protein-to-creatinine ratio, both protein and creatinine were measured in grams. I bars indicate the standard error. A mixed-effects model for repeated measures was used to analyze the percent change in the 24-hour and spot urinary protein-to-creatinine ratio relative to baseline. The mixed-effects model for repeated measures included data assessed on a natural log scale up to week 36, with region (Asia–Pacific vs. the rest of the world), trial group, visit, and trial group–by–visit interaction as fixed effects and baseline estimated glomerular filtration rate and baseline urinary protein-to-creatinine ratio (assessed on a natural log scale) as covariates. Results from the model were back-transformed from a log scale, with percent change from baseline calculated as the estimated geometric mean ratio minus 1, times 100%.

In findings consistent with the mechanism of action of povetacicept on B-cell modulation, serum levels of IgA, IgE, IgG, and IgM had decreased by week 4, had reached a plateau by week 24, and were stable through week 48 in the povetacicept group (Fig. S7). At week 24, the mean percent reduction in IgA, IgE, IgG, and IgM levels was 64.7%, 66.2%, 38.0%, and 80.2%, respectively, with povetacicept. None of the participants discontinued the trial regimen owing to protocol-specified IgG levels below 150 mg per deciliter, and no immune globulin infusions were administered during the trial.

DISCUSSION

Patients with IgA nephropathy are at risk for progression to kidney failure, despite receiving standard-of-care therapy. Because IgA nephropathy is considered to be a B-cell–driven immune-mediated kidney disease caused by IgA-containing immune-complex deposition in glomeruli, BAFF and APRIL appear to be central to the uncontrolled production of galactose-deficient IgA1 and the subsequent immune-complex formation that precedes glomerular deposition and are considered to be pathogenic drivers of IgA nephropathy. Povetacicept, an engineered TACI fusion protein, was designed to bind BAFF and APRIL with high affinity and to have broad tissue distribution and thereby target both upstream immune-complex production and downstream renal inflammation, including intrarenal tertiary lymphoid structures.[15]

In this planned interim analysis of a phase 3 trial, adults with IgA nephropathy who received povetacicept had rapid and significant reductions in proteinuria, galactose-deficient IgA1 levels, and hematuria, which are considered to be key markers of kidney-function preservation in persons with this disease. The incidence of adverse events, including serious adverse events, was similar in the povetacicept and placebo groups. Trial participants were representative of the global population of patients with IgA nephropathy with persistent proteinuria despite receiving stable background therapy, were enrolled across multiple geographic regions and racial and ethnic groups, and had a wide range of baseline disease activity. Treatment effects on proteinuria, galactose-deficient IgA1 levels, and hematuria were observed with a high back-

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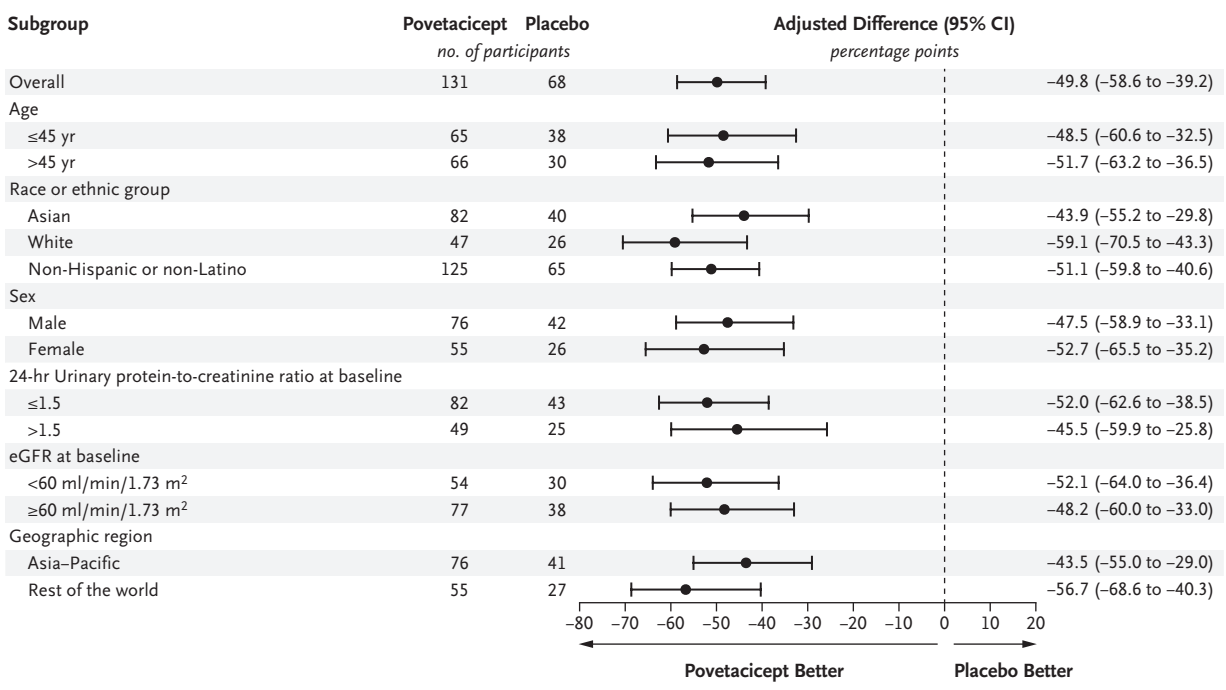

Figure 2. Prespecified Subgroup Analyses of the Primary End Point.

Shown is a forest plot for the prespecified subgroup analyses of the change in the 24-hour urinary protein-to-creatinine ratio from baseline to week 36 (the primary end point). The percent change is based on the adjusted difference between povetacicept and placebo. Race and ethnic group were reported by the participants. For the 24-hour urinary protein-to-creatinine ratio, both protein and creatinine were measured in grams. Confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing. The abbreviation eGFR denotes estimated glomerular filtration rate.

ground use of renin–angiotensin system inhibitors (administered in 97% of participants) and SGLT2 inhibitors (administered in 66% of participants).

The prespecified primary end point and two secondary end points in our trial are considered to be biologically relevant to the pathogenesis of IgA nephropathy. Each of these end points showed significant improvement with povetacicept. Two clinical readouts of kidney injury differed significantly between groups — the change from baseline in 24-hour urinary protein-to-creatinine ratio (the primary end point; adjusted difference, –49.8 percentage points) and resolution of hematuria (a secondary end point; adjusted difference, 62 percentage points). Galactose-deficient IgA1 is considered to be the proximate driver of disease, and the change in galactose-deficient IgA1 levels (a secondary end point) was significantly better with povetacicept than with placebo (adjusted difference, –79.3 percentage points). The concordant reductions in 24-hour urinary protein-to-creatinine ratio and galactose-deficient IgA1 levels support the effect of povetacicept on the underlying biologic features of IgA nephropathy. An exploratory analysis showed that the proteinuria response was observed early in the treatment period, with separation between the trial groups apparent by week 4 and with consistency across all subgroups at week 36. Reductions in galactose-deficient IgA1 levels occurred earlier than the reductions in proteinuria. The proteinuria and galactose-deficient IgA1 response was sustained over the 36-week interim-analysis period. Furthermore, the resolution of hematuria among the participants with hematuria at baseline aligns with the concept of suppression of glomerular inflammation, given that hematuria resolution has been associated with improved long-term outcomes in this subgroup of patients at higher risk for disease progression.[19] These findings are similar to the results of the previous phase 1–2, open-label, uncontrolled,

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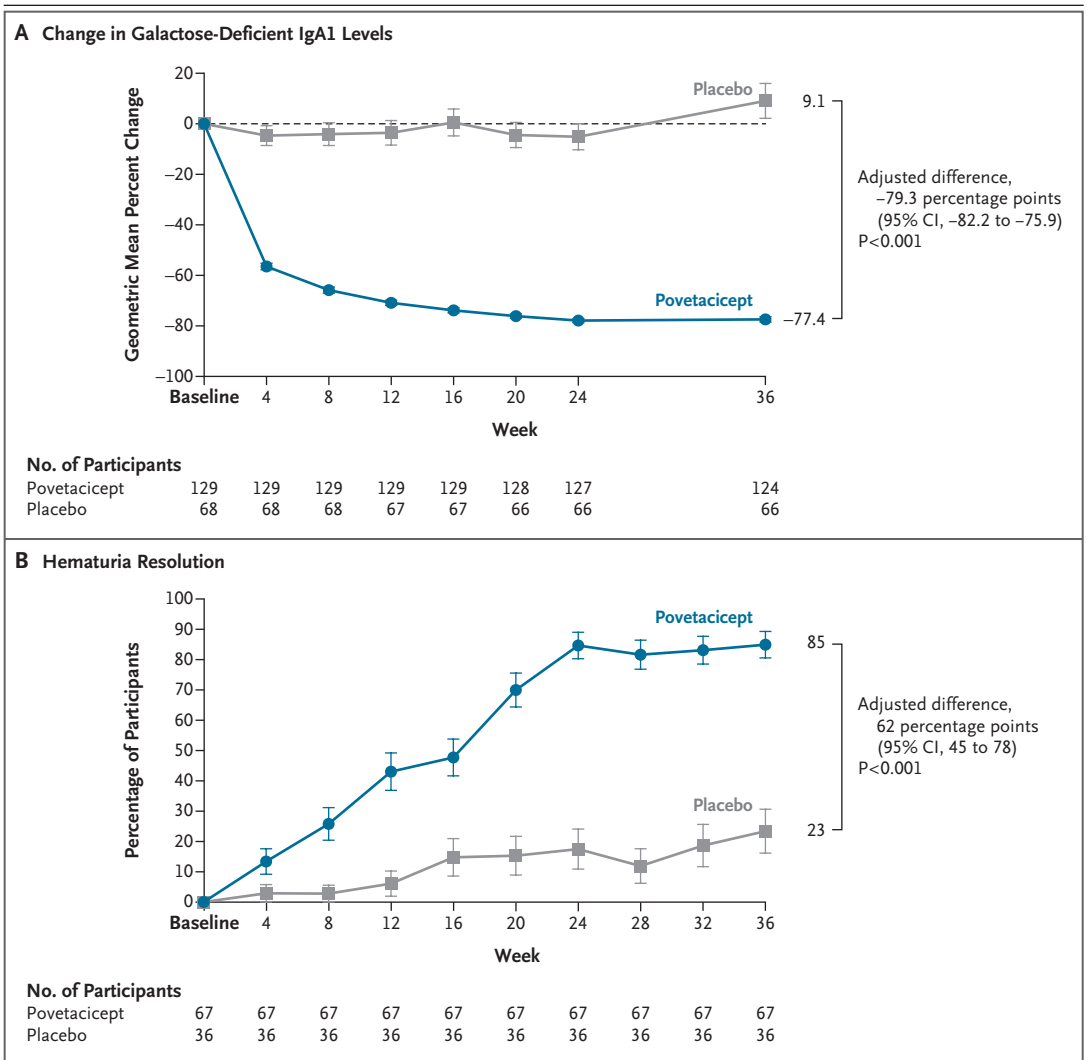

Figure 3. Percent Change in Galactose-Deficient IgA1 Levels and Resolution of Hematuria.

Panel A shows the geometric mean percent change in serum galactose-deficient IgA1 levels at week 36 (multiplicity-controlled secondary end point) and the change over time through week 36. Panel B shows the percentage of participants who had hematuria resolution at week 36 (multiplicity-controlled secondary end point) and the change over time through week 36. Hematuria at baseline was defined as moderate or large amounts of blood in the urine according to a dipstick test. Hematuria resolution was defined as a decrease to no or low levels of blood in the urine of the participants with hematuria at baseline. I bars indicate the standard error.

single-group RUBY-3 study of povetacicept at the same dose.[17]

Reduction in proteinuria is an accepted surrogate end point for kidney outcomes in persons with IgA nephropathy that has supported accelerated approval of multiple therapies by the Food and Drug Administration. In addition, KDIGO guidelines recommend a urinary protein-to-creatinine ratio of less than 0.5 g per day (or equivalent) as a treatment target for patients with IgA nephropathy.[9] In our trial, 24-hour urinary protein-to-creatinine ratios of less than 0.5 and less than 0.3 occurred in more participants who received povetacicept than in those who received placebo.

Administration of povetacicept and placebo led to a similar incidence of adverse events overall. Injection-site reactions were mild in all but one participant, who had a moderate injection-site reaction, and none led to discontinuation of

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

Event	Povetacicept (N = 372)	Placebo (N = 185)
	number of participants (percent)	
Any adverse event	279 (75)	145 (78)
Mild	153 (41)	84 (45)
Moderate	115 (31)	53 (29)
Severe	11 (3)	8 (4)
Infection†	171 (46)	75 (41)
Mild	105 (28)	43 (23)
Moderate	64 (17)	31 (17)
Severe	2 (1)	1 (1)
Any adverse event considered to be related to trial regimen‡	117 (31)	37 (20)
Events occurring in ≥10% of participants in either trial group		
Upper respiratory tract infection	68 (18)	21 (11)
Nasopharyngitis	36 (10)	23 (12)
Injection-site reaction§	54 (15)	4 (2)
Any serious adverse event	11 (3)	8 (4)
Infection	2 (1)	1 (1)
Any adverse event leading to discontinuation of trial regimen¶	1 (<1)	4 (2)
Any adverse event leading to death	0	0

* The safety population consisted of all the participants in the main cohort who underwent randomization and received at least one dose of povetacicept or placebo. One participant was randomly assigned to the placebo group and received one dose of povetacicept in error and was included in the povetacicept group for the safety population.
† Infection was defined according to the *Medical Dictionary for Regulatory Activities*, version 28.1, system organ class of infections and infestations.
‡ The relatedness of the adverse event to the trial regimen was determined by the investigators.
§ Injection-site reactions were identified according to a prespecified set of preferred terms (including, for example, injection-site reaction and injection-site erythema). All injection-site reactions were nonserious. One participant had a moderate injection-site reaction. All other injection-site reactions were mild.
¶ Adverse events leading to discontinuation of the trial regimen included malignant melanoma (stage 0), breast cancer, esophageal carcinoma, suicide attempt, and acute kidney injury.

the trial regimen. Most infections were mild or moderate. The incidence of serious or severe infections was the same in the two trial groups, and none of the infections led to discontinuation of the trial regimen.

This prespecified interim analysis has certain limitations. Given the assessment at week 36, the effects of povetacicept on the annualized eGFR slope and on kidney disease progression, as well as longer-term safety, were prespecified for the final analysis at 104 weeks and were not addressed by these data.

Strengths of this trial include the representativeness of the randomized population with respect to a contemporary population in which IgA nephropathy is prevalent, the prespecified hierarchical testing of three biologically relevant efficacy end points with multiplicity control, and the similar treatment effect on the primary end point across subgroups. Reductions in proteinuria, galactose-deficient IgA1 levels, and hematuria have all been reported to be associated with kidney protection.[19-21] Finally, povetacicept was administered once monthly as a subcutaneous injection, and an autoinjector has been developed for patient administration of a volume of less than 0.5 ml with a 27-gauge needle (ClinicalTrials.gov number, NCT07010406).[22,23]

This prespecified interim analysis of adults with IgA nephropathy showed a sustained reduction in the 24-hour urinary protein-to-creatinine ratio that was significantly greater with povetacicept than with placebo.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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