ORIGINAL ARTICLE

Atacicept in IgA Nephropathy — Phase 3 Trial Final Efficacy Analysis

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ABSTRACT

BACKGROUND

Atacicept resulted in a significantly greater reduction in the urinary protein-to-creatinine ratio than placebo in a previously published analysis of this trial, ORIGIN 3. Final prespecified efficacy results are reported here.

METHODS

We randomly assigned adults with biopsy-confirmed IgA nephropathy to receive weekly subcutaneous atacicept at a dose of 150 mg or placebo. We carried out final analyses of two secondary end points: the change in the estimated glomerular filtration rate (eGFR) at week 52 and the annualized eGFR slope through week 104; additional hierarchically tested end points and safety were assessed.

RESULTS

Of 431 patients who underwent randomization, 428 received atacicept or placebo (214 per group). At week 52, the mean change in the eGFR was −0.11 ml per minute per 1.73 m^2 of body-surface area (95% confidence interval [CI], −1.44 to 1.22) with atacicept and −5.69 ml per minute per 1.73 m^2 (95% CI, −7.04 to −4.35) with placebo (mean difference, 5.58 ml per minute per 1.73 m^2; 95% CI, 3.68 to 7.48; P<0.001). Through week 104, the mean annualized eGFR slope was −0.60 ml per minute per 1.73 m^2 (95% CI, −1.62 to 0.41) with atacicept and −5.60 ml per minute per 1.73 m^2 (95% CI, −6.64 to −4.57) with placebo (difference, 5.00 ml per minute per 1.73 m^2 per year; 95% CI, 3.55 to 6.45; P<0.001). Composite kidney-disease progression occurred in 11 patients (5.1%) in the atacicept group and in 38 patients (17.8%) in the placebo group (hazard ratio, 0.24; 95% CI, 0.12 to 0.48; P<0.001); no patients in the atacicept group had progression to dialysis, transplantation, or death, as compared with 7 patients in the placebo group. Adverse events occurred in 160 of 214 patients (74.8%) in the atacicept group and in 167 of 214 patients (78.0%) in the placebo group; serious adverse events occurred in 7.0% and 15.4%, respectively. One patient (in the placebo group) died.

CONCLUSIONS

Atacicept slowed and stabilized the decline in the eGFR as compared with placebo. (Funded by Vera Therapeutics; ORIGIN 3 ClinicalTrials.gov number, NCT04716231.)

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*A list of investigators and collaborators for the ORIGIN phase 3 trial is provided in the Supplementary Appendix, available at NEJM.org.

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IgA nephropathy is the most common glomerular disease worldwide and is typically diagnosed in young adults.[1-4] Despite supportive care, this disease remains associated with substantial long-term risk of progressive loss of kidney function — at least half of affected patients have kidney failure or die within 10 to 20 years after diagnosis.[5-7] Supportive and kidney-protective therapies can reduce proteinuria and slow disease progression, but many patients remain at risk for continued decline in the estimated glomerular filtration rate (eGFR) and eventual kidney failure.[8-10] Thus, a treatment capable of modifying the underlying disease process and preserving kidney function over time is needed.

A central feature of IgA nephropathy is the mesangial deposition of immune complexes containing galactose-deficient IgA1, which appears to drive glomerular inflammation and progressive nephron loss.[1,11-14] The formation of IgA-containing immune complexes is associated with B-cell and plasma-cell activity, including production of both galactose-deficient IgA1 and anti-glycan antibodies.[1,11-14] B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL), acting primarily through the transmembrane activator and calcium-modulator and cyclophilin-ligand interactor (TACI) receptor, support B-cell and plasma-cell survival, maturation, and IgA class switching and are thought to play central roles in the pathophysiology of IgA nephropathy.[1,11,12,15,16]

Atacicept is a native human TACI–Fc fusion protein that inhibits BAFF and APRIL, thereby modulating B-cell activity and reducing circulating levels of galactose-deficient IgA1, anti-glycan antibodies, and immune complexes.[11,17] By targeting upstream immune mechanisms implicated in disease progression, atacicept may have the potential to affect both biologic drivers of IgA nephropathy and downstream clinical manifestations.[8-10] In the ORIGIN phase 2b trial involving patients with biopsy-confirmed IgA nephropathy, atacicept led to significant reductions in the urinary protein-to-creatinine ratio, which were associated with improvements in disease biomarker results and stabilization of the eGFR through 96 weeks of treatment.[11] In this phase 3 trial, ORIGIN 3, a prespecified interim analysis previously showed that the percentage reduction from baseline in the urinary protein-to-creatinine ratio was 45.7% in the atacicept group and 6.8% in the placebo group at week 36.[18] These results led to the accelerated approval of atacicept by the Food and Drug Administration (FDA) in July 2026.[19] Here, we report the findings from the prespecified final efficacy analysis of the double-blind period, including the change from baseline in the eGFR, the annualized eGFR slope, composite kidney-disease progression, all other end points tested in the fixed-sequence hierarchy, and safety results.

METHODS

TRIAL DESIGN AND PATIENTS

This international, double-blind, randomized, placebo-controlled phase 3 trial evaluated the safety and efficacy of atacicept at a dose of 150 mg once weekly, administered subcutaneously by patients at home, for the treatment of IgA nephropathy (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Adults 18 years of age or older with biopsy-proven IgA nephropathy were randomly assigned in a 1:1 ratio to receive atacicept or matching placebo. Additional inclusion criteria and stratification factors were reported previously.[18] Trial patients were representative of the global population of patients with IgA nephropathy with a demonstrable burden of disease, and the trial population was consistent with those in other trials (Table S1).

TRIAL OVERSIGHT

The trial is overseen by a steering committee of academic investigators in partnership with the sponsor, Vera Therapeutics, which participates in the conduct of the trial and in the analysis and interpretation of the data. The trial was approved by local ethics committees and conducted in accordance with the principles of the Declaration of Helsinki; all the patients provided written informed consent. Details regarding trial oversight, data access, and author responsibilities are provided in the Supplementary Appendix.

END POINTS

The results for the primary efficacy end point, the change from baseline at week 36 in the natural log–transformed urinary protein-to-creatinine ratio from a 24-hour collection, have been published.[18] Key secondary end points in the final efficacy analysis were tested in the following prespecified, fixed-sequence, hierarchical order:

change from baseline in the eGFR at week 52, annualized eGFR slope through week 104, change from baseline at week 52 in the natural log–transformed 24-hour urinary protein-to-creatinine ratio, change from baseline at week 52 in the natural log–transformed serum galactose-deficient IgA1 level, hematuria resolution at week 52 among patients with hematuria at baseline, time to the first sustained decline in the eGFR of at least 30% through week 104, and time to the first composite kidney-disease progression event (defined below) through week 104. The safety analysis included all the patients who had undergone randomization and received at least one dose of atacicept or placebo. Safety data were summarized descriptively. Exploratory end points included the change from baseline in immunoglobulin biomarkers (IgA, IgG, and IgM). Immunogenicity was assessed by measuring antidrug antibodies to atacicept.

On the basis of alignment with the FDA on May 19, 2026, including an assessment of the ORIGIN phase 2b 96-week eGFR results, the protocol and statistical analysis plan of the present trial (available at NEJM.org) were revised to conduct the final efficacy analysis of the change from baseline in the eGFR at week 52 (rather than at week 104) along with the annualized eGFR slope through week 104. This change allowed the final efficacy analysis to be conducted earlier to assess the treatment effect of atacicept in IgA nephropathy and enable earlier transition of patients to open-label atacicept.

STATISTICAL ANALYSIS

Efficacy analyses were performed in the full analysis population, which included all the patients who had undergone randomization and had received at least one dose of atacicept or placebo. A prespecified fixed-sequence procedure (Fig. S2) controlled the overall type I error at a two-sided alpha level of 0.05. Because the between-group difference for the primary end point met the prespecified criterion for significance, the key secondary end points were tested sequentially at the 0.05 level. The change from baseline in the eGFR at week 52 was analyzed with a mixed-effects model for repeated measures. The eGFR was calculated with the use of the prespecified Chronic Kidney Disease Epidemiology Collaboration 2009 creatinine equation,[20] including the race coefficient. The model included baseline eGFR, trial group, visit, trial-group-by-visit interaction, and the stratification factors of use of a stable sodium–glucose cotransporter 2 (SGLT2) inhibitor at baseline, geographic region, and category of total urinary excretion of protein at baseline. An unstructured covariance matrix was used. Results from 100 imputed datasets were combined with Rubin's rules,[21] and treatment effects were reported with two-sided 95% confidence intervals and P values.

In the prespecified analysis, intercurrent events included discontinuation of the trial regimen, initiation of rescue or prohibited therapy without acute effects on the eGFR, initiation of immunosuppressive treatment with acute effects on the eGFR, and dialysis, kidney transplantation, or death. A treatment policy strategy was used for discontinuation of the trial regimen and initiation of rescue or prohibited therapy without acute effects on the eGFR. Data after immunosuppressive treatment with acute effects on the eGFR were imputed with a jump-to-reference approach, and data after dialysis, kidney transplantation, or death were imputed with a sufficiently unfavorable value plus random error. Missing values after discontinuation of the trial regimen or after initiation of rescue or prohibited therapy without acute effects on the eGFR were imputed with a jump-to-reference approach; other missing values were imputed under a missing-at-random assumption. Prespecified sensitivity analyses evaluated the robustness of the results with alternative approaches to handling intercurrent events and missing-data assumptions. We also conducted a post hoc intention-to-treat analysis in which all randomly assigned patients were included and all intercurrent events were handled with a treatment policy approach.

The annualized eGFR slope through week 104 was estimated with a mixed-effects model with random intercept and slope. The model included trial group, time, trial-group-by-time interaction, and the stratification factors. Results from 100 imputed datasets were combined with Rubin's rules,[21] and the slope difference was reported with a two-sided 95% confidence interval and P value.

Changes in the urinary protein-to-creatinine ratio and galactose-deficient IgA1 level at week 52 were analyzed on the natural log scale with mixed-effects models for repeated measures, and results were back-transformed to provide percentage reductions relative to placebo. Hematuria resolution was analyzed with repeated-measures

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Atacicept (N=214)	Placebo (N=214)
Median age (range) — yr	41 (18–74)	42 (18–70)
Sex — no. (%)		
Male	122 (57.0)	132 (61.7)
Female	92 (43.0)	82 (38.3)
Race or ethnic group — no. (%)†		
American Indian or Alaska Native	0	0
Asian	117 (54.7)	114 (53.3)
Black or African American	0	1 (0.5)
Native Hawaiian or other Pacific Islander	0	2 (0.9)
White	94 (43.9)	95 (44.4)
Other	2 (0.9)	2 (0.9)
Unknown or not reported	1 (0.5)	0
Hispanic or Latino	27 (12.6)	16 (7.5)
Non-Hispanic or non-Latino	187 (87.4)	198 (92.5)
Hematuria — no. (%)‡		
Negative or trace amount of blood	75 (35.0)	74 (34.6)
1+	45 (21.0)	41 (19.2)
2+	56 (26.2)	48 (22.4)
3+	38 (17.8)	51 (23.8)
Urinary protein-to-creatinine ratio§	1.6±0.9	1.6±1.0
Estimated glomerular filtration rate — ml/min/1.73 m^2	64.5±27.4	62.9±26.6
Urinary protein excretion — g/day	2.2±1.1	2.2±1.2
Urinary albumin-to-creatinine ratio§	1.2±0.7	1.2±0.8
Galactose-deficient IgA1 — μg/liter	5523.6±5018.2	5006.6±2664.4
IgA — mg/dl	354.7±129.9	340.5±111.9
IgG — mg/dl	1207.8±280.9	1150.0±288.9
IgM — mg/dl	104.4±52.5	103.5±57.9
Blood pressure — mm Hg		
Systolic	124.1±11.1	124.6±11.0
Diastolic	79.7±8.3	78.4±8.1
Stable use of SGLT2 inhibitor — no. (%)	134 (62.6)	129 (60.3)
Use of RAS inhibitor — no. (%)	210 (98.1)	212 (99.1)
Time since biopsy — yr¶	2.6±2.6	2.3±2.4

* Plus–minus values are means ±SD. RAS denotes renin–angiotensin system, and SGLT2 sodium–glucose cotransporter 2.
† Race and ethnic group were reported by the patients.
‡ Hematuria was determined by a dipstick reading of at least 1+.
§ For these measures, protein, albumin, and creatinine were measured in grams.
¶ Eligibility was not restricted on the basis of Oxford Classification MEST-C histopathologic score.

logistic regression. Composite kidney-disease progression was defined as a decline in the eGFR of at least 30% that was sustained for at least 30 days, a sustained eGFR of less than 15 ml per minute per 1.73 m^2 of body-surface area, long-term dialysis, kidney transplantation, or death. Time to a sustained decline in the eGFR of at least 30% and time to composite kidney-disease progression were

Table 2. Key Secondary Efficacy End Points.*

End Point	Atacicept (95% CI)	Placebo (95% CI)	Treatment Effect (95% CI)†	P Value
Change from baseline in eGFR at wk 52, prespecified analysis				
No. of patients for end-point evaluation	214	214	—	—
Mean change — ml/min/1.73 m^2	−0.11 (−1.44 to 1.22)	−5.69 (−7.04 to −4.35)	5.58 (3.68 to 7.48)	<0.001
Change from baseline in eGFR at wk 52, post hoc intention-to-treat analysis‡				
No. of patients for end-point evaluation	216	215	—	—
Mean change — ml/min/1.73 m^2	0.08 (−1.22 to 1.38)	−5.26 (−6.57 to −3.96)	5.34 (3.50 to 7.19)	—
Annualized eGFR slope through wk 104, prespecified analysis				
No. of patients for end-point evaluation	214	214	—	—
Mean slope — ml/min/1.73 m^2/yr	−0.60 (−1.62 to 0.41)	−5.60 (−6.64 to −4.57)	5.00 (3.55 to 6.45)	<0.001
Annualized eGFR slope through wk 104, post hoc intention-to-treat analysis‡				
No. of patients for end-point evaluation	216	215	—	—
Mean slope — ml/min/1.73 m^2/yr	−0.46 (−1.39 to 0.47)	−4.61 (−5.55 to −3.67)	4.15 (2.82 to 5.47)	—
Change from baseline in 24-hr urinary protein-to-creatinine ratio at wk 52§				
No. with observed wk 52 data	203	192	—	—
Percentage reduction from baseline	53.3 (48.6 to 57.6)	4.7 (−5.0 to 13.5)¶	51.0 (43.8 to 57.3)	<0.001
Change from baseline in serum galactose-deficient IgA1 level at wk 52§				
No. with observed wk 52 data	201	198	—	—
Percentage reduction from baseline	66.1 (64.0 to 68.0)	−2.9 (−9.1 to 3.0)¶	67.0 (64.5 to 69.4)	<0.001
Hematuria resolution at wk 52‖				
No. with resolution/total no. with available data (%)	106/131 (80.9)	28/131 (21.4)	—	—
Estimated probability — %	81.3 (73.7 to 87.1)	21.0 (14.9 to 28.8)	16.4 (8.9 to 30.0)	<0.001
Sustained decline in eGFR of ≥30% through wk 104**				
No. of patients with event/total no. (%)	11/214 (5.1)	38/214 (17.8)	0.24 (0.12 to 0.47)	<0.001
Composite kidney-disease progression through wk 104††				
No. of patients with event/total no. (%)	11/214 (5.1)	38/214 (17.8)	0.24 (0.12 to 0.48)	<0.001

* The key secondary end points were evaluated in the full analysis population (214 patients in each group) and are presented in the prespecified fixed-sequence hierarchical order. The between-group difference for all the end points met the prespecified criterion for significance, which permitted formal testing to continue through the hierarchy. CI denotes confidence interval, and eGFR estimated glomerular filtration rate.

† The treatment effect is reported as the between-group difference for the eGFR end points, the adjusted difference in percentage points for the urinary protein-to-creatinine ratio and galactose-deficient IgA1 end points, an odds ratio for hematuria resolution, and a hazard ratio for the time-to-event end points.

‡ A treatment-policy strategy was used for all intercurrent events, including data collected after discontinuation of the trial regimen, initiation of rescue or prohibited therapy, dialysis, or kidney transplantation. No multiple imputations were performed. A P value was not reported for this post hoc analysis.

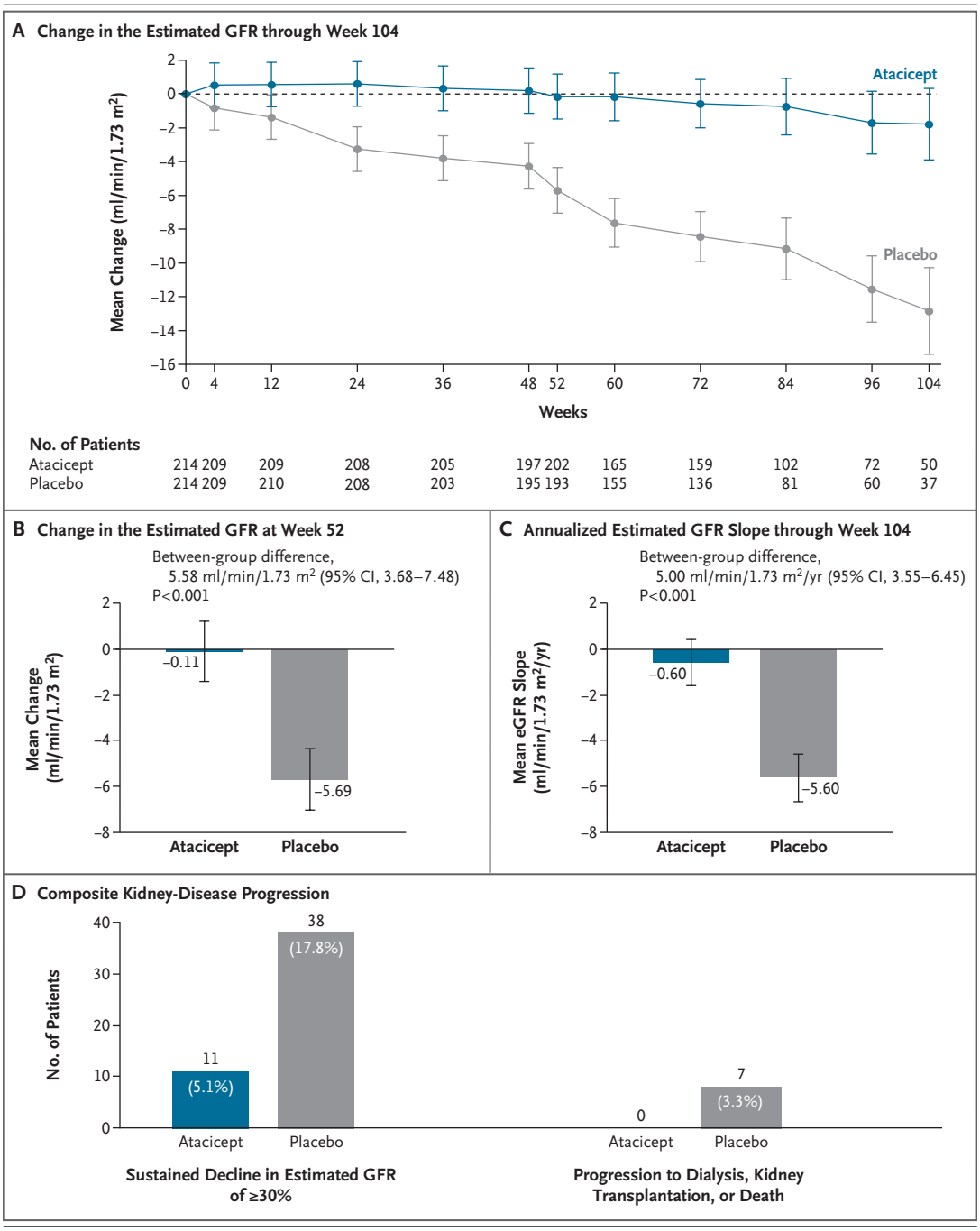
§ The natural log–transformed ratio to baseline was analyzed with a mixed-effects model for repeated measures. The adjusted difference in percentage points was derived from the ratio of geometric least-squares means.

¶ A negative value denotes an increase from baseline.

‖ Hematuria resolution was defined as improvement from a dipstick result of 1+, 2+, or 3+ at baseline to a negative or trace result at week 52. The percentages in the second row are model-estimated probabilities.

** A sustained decline in the eGFR was defined as a decrease of at least 30% from baseline that was maintained for at least 30 days.

†† Composite kidney-disease progression was defined as the first occurrence of a sustained decline in the eGFR of at least 30%, a sustained eGFR of less than 15 ml per minute per 1.73 m^2, long-term dialysis (≥30 days), kidney transplantation, or death.



analyzed with Cox proportional-hazards models. These models included the stratification factors, and treatment effects were reported with two-sided 95% confidence intervals and P values.

Exploratory pharmacodynamic analyses were not controlled for multiplicity. Immunogenicity analyses were conducted with the use of descriptive statistics. Safety analyses included all the patients who had received at least one dose of atacicept or placebo, according to the intervention received, and were summarized descriptively.

RESULTS

PATIENTS

A total of 750 patients were screened; 431 underwent randomization, and 428 received the assigned intervention (214 in the atacicept group and 214

Figure 1 (facing page). Mean Change in Estimated GFR, Annualized Estimated GFR Slope, and Composite Kidney-Disease Progression.

Panel A shows the mean change in the estimated glomerular filtration rate (GFR) from baseline through week 104 for atacicept and placebo. The numbers below the x axis represent patients with available measurements at each visit. Panel B shows the mean change in the estimated GFR from baseline to week 52 for atacicept and placebo and the between-group difference. Panel C shows the annualized estimated GFR slope through week 104 for atacicept and placebo and the between-group difference. I bars indicate 95% confidence intervals. Panel D shows the number and percentage of patients who had a reduction from baseline in the estimated GFR of at least 30% that was sustained for at least 30 days and those who had progression to dialysis, kidney transplantation, or death (not including one patient in the placebo group who received transient dialysis for acute kidney injury). The prespecified week 52 end-point estimates are from analyses including data through week 52, and week 104 end-point estimates are from analyses including data through week 104.

in the placebo group) and were included in the full analysis and safety populations (Fig. S3). At the data-cutoff date of June 10, 2026, a total of 199 patients (93.0%) in the atacicept group and 169 (79.0%) in the placebo group continued to receive the trial agent. Through week 104, discontinuation of the trial regimen occurred in 15 patients (7.0%) in the atacicept group and in 45 (21.0%) in the placebo group. The demographic and clinical characteristics of the patients at baseline were generally balanced between the two groups (Table 1 and Table S2). The median age was 41 years, 59.3% of the patients were men, and the mean (±SD) eGFR at baseline was 63.7±27.0 ml per minute per 1.73 m^2.

EFFICACY

The results for the primary end point were reported previously.[18] The results for key secondary efficacy end points in hierarchical order are shown in Table 2. All the key secondary end points in the fixed-sequence hierarchy showed a significant treatment effect.

At week 52, in the prespecified analysis, the between-group difference in the mean change from baseline in the eGFR was 5.58 ml per minute per 1.73 m^2 (95% confidence interval [CI], 3.68 to 7.48; P<0.001), with a mean change of −0.11 ml per minute per 1.73 m^2 (95% CI, −1.44 to 1.22) in the atacicept group and −5.69 ml per minute per 1.73 m^2 (95% CI, −7.04 to −4.35) in the placebo group (Fig. 1A and 1B). The between-group difference in the annualized eGFR slope through week 104 was 5.00 ml per minute per 1.73 m^2 per year (95% CI, 3.55 to 6.45; P<0.001), with a slope of −0.60 ml per minute per 1.73 m^2 per year (95% CI, −1.62 to 0.41) with atacicept and −5.60 ml per minute per 1.73 m^2 per year (95% CI, −6.64 to −4.57) with placebo (Fig. 1C). At week 52, an intention-to-treat analysis showed the mean change in the eGFR was 0.08 ml per minute per 1.73 m^2 (95% CI, −1.22 to 1.38) with atacicept and −5.26 ml per minute per 1.73 m^2 (95% CI, −6.57 to −3.96) with placebo, for a mean difference of 5.34 ml per minute per 1.73 m^2 (95% CI, 3.50 to 7.19). The intention-to-treat between-group difference in the annualized eGFR slope through week 104 was 4.15 ml per minute per 1.73 m^2 per year (95% CI, 2.82 to 5.47), with a slope of −0.46 ml per minute per 1.73 m^2 per year (95% CI, −1.39 to 0.47) with atacicept and −4.61 ml per minute per 1.73 m^2 per year (95% CI, −5.55 to −3.67) with placebo. Results of the sensitivity analyses were consistent with those of the primary analysis (Table S3).

At week 52, the 24-hour urinary protein-to-creatinine ratio was reduced from baseline by 53% with atacicept and by 5% with placebo, which corresponded to an adjusted difference of 51 percentage points (95% CI, 44 to 57; P<0.001) (Fig. S4). The serum galactose-deficient IgA1 level decreased by 66% with atacicept and increased by 3% with placebo (adjusted difference, 67 percentage points; 95% CI, 65 to 69; P<0.001). Among patients with hematuria at baseline, resolution at week 52 occurred in 106 of 131 patients (80.9%) receiving atacicept and in 28 of 131 patients (21.4%) receiving placebo (odds ratio, 16.4; 95% CI, 8.9 to 30.0; P<0.001) (Fig. S5).

Composite kidney-disease progression through week 104 occurred in 11 patients (5.1%) in the atacicept group and in 38 (17.8%) in the placebo group (hazard ratio, 0.24; 95% CI, 0.12 to 0.48; P<0.001) (Fig. 1D). All the patients who had composite events first had a sustained decline in the eGFR of at least 30%. Among the 38 placebo recipients with a composite event, 7 subsequently had progression to dialysis, kidney transplantation, or death; no atacicept recipients had progression to dialysis, kidney transplantation, or death (Table S4).

Results were similar across all prespecified

Subgroup	Total No. of Patients (%)	Mean Change Atacicept ml/min/1.73 m²	Mean Change Placebo ml/min/1.73 m²	Between-Group Difference (95% CI) ml/min/1.73 m²
Overall	428 (100)	−0.11	−5.69	5.58 (3.68–7.48)
Age				
<40 yr	189 (44)	−1.66	−8.22	6.56 (3.57–9.56)
≥40 yr	239 (56)	1.09	−3.65	4.74 (2.38–7.10)
Sex				
Male	254 (59)	−1.08	−5.83	4.76 (2.35–7.16)
Female	174 (41)	1.15	−5.46	6.61 (3.56–9.66)
Geographic region				
Americas, Australia, and Europe	218 (51)	0.80	−4.63	5.43 (3.01–7.84)
Asia	210 (49)	−1.09	−6.76	5.68 (2.79–8.56)
Race or ethnic group				
White	189 (44)	0.89	−4.31	5.20 (2.60–7.80)
Non-White	238 (56)	−0.90	−6.79	5.90 (3.24–8.55)
Urinary protein-to-creatinine ratio at baseline				
<1.5	233 (54)	0.37	−3.16	3.53 (1.13–5.93)
≥1.5	195 (46)	−0.70	−8.63	7.93 (5.02–10.84)
Estimated GFR at baseline				
<45 ml/min/1.73 m²	128 (30)	−1.22	−6.43	5.22 (2.57–7.86)
≥45 ml/min/1.73 m²	300 (70)	0.45	−5.46	5.91 (3.46–8.35)
<60 ml/min/1.73 m²	227 (53)	−0.15	−5.80	5.65 (3.41–7.89)
≥60 ml/min/1.73 m²	201 (47)	−0.13	−5.50	5.36 (2.25–8.48)
SGLT2 inhibitor use at baseline				
Yes	263 (61)	0.57	−5.40	5.97 (3.64–8.30)
No	165 (39)	−1.28	−6.12	4.84 (1.62–8.06)

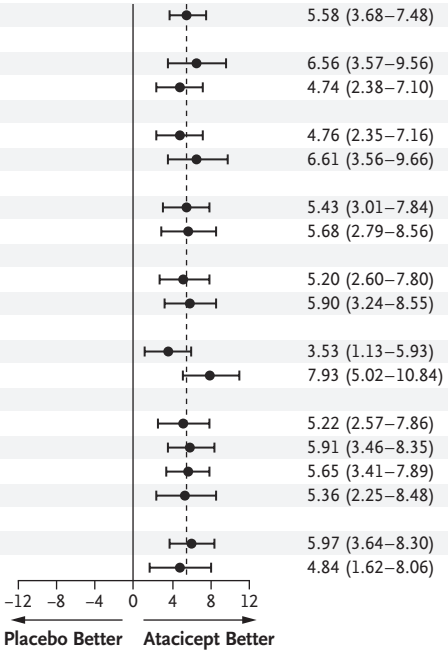


Figure 2. Change in the Estimated GFR at Week 52 across Prespecified Subgroups.

For each prespecified subgroup, analyses were performed separately for each subgroup category with the same imputed datasets and mixed-effects model for repeated measures as the primary analysis; if the subgroup variable was a covariate in the primary model, it was omitted from the subgroup-specific model. The confidence intervals for the subgroup analyses were not adjusted for multiplicity and should not be used in place of hypothesis testing; thus, no conclusions regarding individual subgroups can be made. Race and ethnic group were reported by the patients; non-White includes Asian, Black or African American, Native Hawaiian or other Pacific Islander, or other. For the urinary protein-to-creatinine ratio, both protein and creatinine were measured in grams. SGLT2 denotes sodium–glucose cotransporter 2.

subgroups, including subgroups defined according to age, sex, race or ethnic group, geographic region, baseline eGFR, baseline urinary protein-to-creatinine ratio, and baseline SGLT2 inhibitor use. For details, see Figure 2 and Figure S6.

SAFETY

Adverse events occurred in 160 patients (74.8%) receiving atacicept and in 167 (78.0%) receiving placebo; most events were mild or moderate in severity (Table 3). Serious adverse events occurred in 15 patients (7.0%) receiving atacicept and in 33 (15.4%) receiving placebo, and adverse events led to discontinuation of the trial regimen in 4 patients (1.9%) receiving atacicept and in 22 (10.3%) receiving placebo.

The incidence of infection was similar in the two groups, with infection occurring in 110 patients (51.4%) receiving atacicept and in 112 (52.3%) receiving placebo; serious or severe infections occurred in 6 patients (2.8%) and in 8 patients (3.7%), respectively. There were no occurrences of opportunistic infections or clinically relevant hypogammaglobulinemia. Injection-site reactions occurred in 65 patients (30.4%) receiving atacicept and in 16 (7.5%) receiving placebo; all were mild or moderate. Adverse events that were considered by the investigator to be related to the trial regimen occurred in 75 patients (35.0%) receiving atacicept and in 38 (17.8%) receiving placebo and primarily reflected injection-site reactions. Hypersensitivity reactions occurred in 21 patients (9.8%) and in 23 patients (10.7%), respectively. No patient receiving atacicept died;

Table 3. Adverse Events (Safety Analysis Population).*

Event	Atacicept (N=214)	Placebo (N=214)
	no. of patients (%)	
Any adverse event	160 (74.8)	167 (78.0)
Mild	97 (45.3)	100 (46.7)
Moderate	56 (26.2)	48 (22.4)
Severe	7 (3.3)	19 (8.9)
Adverse events occurring in ≥5% of the patients in either group		
Injection-site reaction	42 (19.6)	8 (3.7)
Upper respiratory tract infection	34 (15.9)	44 (20.6)
Nasopharyngitis	27 (12.6)	27 (12.6)
Headache	16 (7.5)	10 (4.7)
Hypertension	14 (6.5)	11 (5.1)
Injection-site erythema	14 (6.5)	0
Dizziness	13 (6.1)	4 (1.9)
Influenza	13 (6.1)	9 (4.2)
Cough	8 (3.7)	16 (7.5)
Peripheral edema	8 (3.7)	16 (7.5)
Diarrhea	7 (3.3)	15 (7.0)
Back pain	7 (3.3)	14 (6.5)
Proteinuria	3 (1.4)	11 (5.1)
Any adverse event related to the trial regimen†	75 (35.0)	38 (17.8)
Mild	64 (29.9)	26 (12.1)
Moderate	11 (5.1)	9 (4.2)
Severe	0	3 (1.4)
Any serious adverse event‡	15 (7.0)	33 (15.4)
Any adverse event related to infection or infestation	110 (51.4)	112 (52.3)
Mild	80 (37.4)	85 (39.7)
Moderate	29 (13.6)	24 (11.2)
Severe	1 (0.5)	3 (1.4)
Any serious adverse event related to infection or infestation	6 (2.8)	8 (3.7)
Any adverse event associated with injection-site reactions§	65 (30.4)	16 (7.5)
Mild	59 (27.6)	14 (6.5)
Moderate	6 (2.8)	2 (0.9)
Severe	0	0
Any adverse event related to the trial regimen and associated with injection-site reactions†	54 (25.2)	16 (7.5)
Any adverse event leading to interruption of the trial regimen	11 (5.1)	17 (7.9)
Any adverse event leading to discontinuation of the trial regimen	4 (1.9)	22 (10.3)
Any adverse event leading to death	0	1 (0.5)¶

* The safety analyses included all the patients who had undergone randomization and had received at least one dose of atacicept or placebo. Safety data were summarized with the use of descriptive statistics.
† The relatedness of adverse events to the trial regimen was determined by the investigator.
‡ Among patients in the placebo group with serious adverse events, seven had events characterized as kidney or urinary disorders. Additional laboratory-assessed events included a decreased eGFR in two patients and an increased blood creatinine level in one patient. There were no serious adverse events involving kidney or urinary disorders or kidney-related laboratory-assessed serious adverse events in the atacicept group.
§ Adverse events associated with injection-site reactions included those coded as 17 prespecified preferred terms under the high-level term of "injection-site reactions," according to the *Medical Dictionary for Regulatory Activities*, version 27.1.
¶ High-grade B-cell lymphoma led to death in one patient in the placebo group.

1 patient receiving placebo died. Serum IgA, IgG, and IgM concentrations decreased early after the initiation of atacicept, and these reductions were maintained through week 104, findings that were consistent with the mechanism of action of the drug (Fig. S7). Antidrug antibodies were detected in 102 of 214 atacicept recipients (47.7%) and in 3 of 211 placebo recipients (1.4%). No clinically meaningful effect of antidrug antibodies on efficacy or overall safety was identified in descriptive analyses.

DISCUSSION

This final efficacy analysis showed significant treatment effects across all end points assessed in a prespecified fixed-sequence hierarchy. These effects included stabilization of kidney function and a significantly lower risk of composite kidney-disease progression with atacicept than with placebo.

The general evolution of therapies for chronic kidney disease provides context for the magnitude of kidney protection observed with atacicept as compared with placebo. For more than three decades, efforts to slow the progression of chronic kidney disease have transformed clinical care, first with renin–angiotensin system inhibition and more recently with SGLT2 inhibitors and other kidney-protective therapies.[8-10,22,23] Across landmark trials, reductions of approximately 16 to 55% in composite kidney outcomes have generally been reported. In the present trial, treatment with atacicept resulted in a 76% lower estimated risk of composite kidney-disease progression through week 104, which represents a clinically meaningful treatment effect among outcomes reported not only in IgA nephropathy but across contemporary phase 3 trials of chronic kidney disease. Despite relatively short follow-up, there was an absence of progression to dialysis, kidney transplantation, or death among patients who received atacicept, as compared with seven such events in the placebo group in this trial.

A benefit with respect to kidney-disease progression was coupled with substantial eGFR stabilization with atacicept. At week 52, the between-group difference in the mean change in the eGFR was 5.58 ml per minute per 1.73 m^2. The between-group difference in the annualized eGFR slope through week 104 was 5.00 ml per minute per 1.73 m^2, with slopes of −0.60 ml per minute per 1.73 m^2 per year with atacicept and −5.60 ml per minute per 1.73 m^2 per year with placebo. The slope in the atacicept group meets the 2025 Kidney Disease: Improving Global Outcomes goal of a decline of less than 1 ml per minute per 1.73 m^2 per year.[24]

The timing of this final efficacy analysis was revised on May 19, 2026, in alignment with FDA requests. As the therapeutic landscape has evolved, prolonged placebo-controlled follow-up has become increasingly challenging for patients with progressive IgA nephropathy. Accordingly, this trial included an earlier FDA-aligned confirmatory assessment of the eGFR, which represents an evolution in trial methods.

In this trial, results for all end points in the fixed-sequence hierarchy met prespecified criteria for significance. These findings are also consistent with those from the ORIGIN phase 2b trial and the previous prespecified interim analysis of the present trial, in which atacicept reduced the urinary protein-to-creatinine ratio, was associated with stabilization of kidney function, and decreased galactose-deficient IgA1 levels and hematuria. The consistency across development phases, populations, and efficacy measures strengthens the evidence supporting atacicept as a disease-modifying treatment for IgA nephropathy.[11,18,19]

Adverse events occurred at similar frequencies with atacicept and placebo and were predominantly mild or moderate; serious adverse events and adverse events leading to discontinuation of the trial regimen were less frequent with atacicept than with placebo. Furthermore, there was no reported clinical evidence of overimmunosuppression. Expected reductions in serum immunoglobulin concentrations were not accompanied by increased infections as compared with placebo. In the atacicept group, there were no opportunistic infections, cases of clinically relevant hypogammaglobulinemia, or deaths, findings consistent with the safety profile previously observed with atacicept in patients with IgA nephropathy.

Strengths of the trial include its randomized, placebo-controlled design; broad international enrollment; and the inclusion of patients receiving appropriate contemporary supportive care (61.4% were receiving stable SGLT2 inhibitor therapy at baseline). The limitations of the trial include the exclusion of certain high-risk populations such as patients with recurrent IgA nephropathy after kidney transplantation. The efficacy and safety of

atacicept in this population are being evaluated in an ongoing study, with results awaited (ClinicalTrials.gov number, NCT06674577).[25] In addition, the initiation of therapies that were recently approved for IgA nephropathy was prohibited during the double-blind period, and the trial did not include an active comparator (e.g., complement inhibitor).

Atacicept showed significant effects across all prespecified end points, reducing proteinuria, slowing eGFR loss, lowering galactose-deficient IgA1 levels, decreasing hematuria, and reducing the risk of kidney-disease progression, with safety results similar to those with placebo. This alignment of mechanistic, clinical, and kidney outcome measures suggests that upstream BAFF and APRIL inhibition with atacicept may provide kidney-protective therapy in IgA nephropathy

In this trial, atacicept slowed and stabilized the decline in the eGFR as compared with placebo.

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REFERENCES

1. Barratt J, Feehally J. IgA nephropathy. J Am Soc Nephrol 2005;16:2088-97.
2. Kwon CS, Daniele P, Forsythe A, Ngai C. A systematic literature review of the epidemiology, health-related quality of life impact, and economic burden of immunoglobulin A nephropathy. J Health Econ Outcomes Res 2021;8:36-45.
3. Moriyama T, Tanaka K, Iwasaki C, et al. Prognosis in IgA nephropathy: 30-year analysis of 1,012 patients at a single center in Japan. PLoS One 2014;9(3):e91756.
4. Heerspink HJL, Jardine M, Kohan DE, et al. Atrasentan in patients with IgA nephropathy. N Engl J Med 2025;392:544-54.
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. Hastings MC, Bursac Z, Julian BA, et al. Life expectancy for patients from the southeastern United States with IgA nephropathy. Kidney Int Rep 2017;3:99-104.
7. Jarrick S, Lundberg S, Welander A, et al. Mortality in IgA nephropathy: a nationwide population-based cohort study. J Am Soc Nephrol 2019;30:866-76.
8. Wheeler DC, Stefánsson BV, Jongs N, et al. Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney disease: a prespecified analysis from the DAPA-CKD trial. Lancet Diabetes Endocrinol 2021;9:22-31.
9. Rovin BH, Barratt J, Heerspink HJL, et al. Efficacy and safety of sparsentan versus irbesartan in patients with IgA nephropathy (PROTECT): 2-year results from a randomised, active-controlled, phase 3 trial. Lancet 2023;402:2077-90.
10. Lafayette R, Kristensen J, Stone A, et al. Efficacy and safety of a targeted-release formulation of budesonide in patients with primary IgA nephropathy (NefIgArd): 2-year results from a randomised phase 3 trial. Lancet 2023;402:859-70.
11. Lafayette R, Barbour S, Israni R, et al. A phase 2b, randomized, double-blind, placebo-controlled, clinical trial of atacicept for treatment of IgA nephropathy. Kidney Int 2024;105:1306-15.
12. Lai KN, Tang SCW, Schena FP, et al. IgA nephropathy. Nat Rev Dis Primers 2016; 2:16001.
13. 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.
14. Suzuki H, Kiryluk K, Novak J, et al. The pathophysiology of IgA nephropathy. J Am Soc Nephrol 2011;22:1795-803.
15. Mackay F, Schneider P, Rennert P, Browning J. BAFF AND APRIL: a tutorial on B cell survival. Annu Rev Immunol 2003;21: 231-64.
16. Mackay F, Ambrose C. The TNF family members BAFF and APRIL: the growing complexity. Cytokine Growth Factor Rev 2003;14:311-24.
17. 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.
18. Lafayette R, Barbour SJ, Brenner RM, et al. A phase 3 trial of atacicept in patients with IgA nephropathy. N Engl J Med 2026;394:647-57.
19. Barratt J, Barbour SJ, Brenner RM, et al. Long-term results from an open-label extension study of atacicept for the treatment of IgA nephropathy. J Am Soc Nephrol 2025;36:679-87.
20. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150: 604-12.
21. Multiple imputation. In: van Buuren S. Flexible imputation of missing data. 2nd

ed. Boca Raton, FL: CRC Press, 2018:29-62.
22. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861-9.
23. Barratt J, Eren N, Kashihara N, et al. Iptacopan in IgA nephropathy — final 24-month data. N Engl J Med 2026;395:465-77.
24. Floege J, Barratt J, Cook HT, et al. Executive summary of the KDIGO 2025 clinical practice guideline for the management of immunoglobulin A nephropathy (IgAN) and immunoglobulin A vasculitis (IgAV). Kidney Int 2025;108:548-54.
25. Gill J, Lafayette R, Barratt J, et al. Studying post-transplant IgA nephropathy in PIONEER, a basket trial of atacicept in autoimmune glomerular disease. Am J Transplant 2026;26:S673. abstract (https://www.amjtransplant.org/article/S1600-6135(26)01668-0/fulltext).
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