ORIGINAL ARTICLE

A Phase 3 Trial of Atacicept in Patients with IgA Nephropathy

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ABSTRACT

BACKGROUND

IgA nephropathy, the most common primary glomerulopathy worldwide, is a kidney disorder of B-cell origin characterized by mesangial accumulation of IgA-containing immune complexes. In at least 50% of patients, IgA nephropathy leads to kidney failure or death within 10 to 20 years after diagnosis. Atacicept is a native human transmembrane activator and calcium-modulator and cyclophilin-ligand interactor (TACI)–Fc fusion protein that inhibits two key immunoregulatory cytokines — B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) — that are thought to be central to the pathophysiology of IgA nephropathy.

METHODS

In this ongoing, phase 3, multicenter, double-blind, randomized, placebo-controlled trial, we assigned patients with IgA nephropathy in a 1:1 ratio to receive atacicept at a dose of 150 mg once weekly, administered subcutaneously by patients at home, or matching placebo. The primary end point was the percentage change from baseline in the 24-hour urinary protein-to-creatinine ratio at week 36. Safety was also evaluated.

RESULTS

A total of 203 patients were included in the prespecified interim analysis: 106 patients in the atacicept group and 97 in the placebo group. At week 36, 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, with a geometric mean between-group difference of 41.8 percentage points (95% confidence interval, 28.9 to 52.3; P<0.001). Adverse events were observed in 59.3% of the patients in the atacicept group and in 50.0% in the placebo group; most were mild or moderate in severity.

CONCLUSIONS

In this prespecified interim analysis, treatment with atacicept resulted in a significantly greater reduction in proteinuria than placebo at week 36 in patients with IgA nephropathy. (Funded by Vera Therapeutics; ORIGIN 3 ClinicalTrials.gov number, NCT04716231.)

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*A list of investigators and collaborators for the ORIGIN 3 trial is provided in the Supplementary Appendix.

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IgA nephropathy, which is most often diagnosed in young adulthood, is the most common primary glomerulopathy, with an estimated worldwide incidence of 2.5 cases per 100,000 persons per year among adults.[1-4] In at least 50% of patients, IgA nephropathy progresses to kidney failure or death within 10 to 20 years after diagnosis.[5-7] Despite recent therapeutic advances for IgA nephropathy, available treatments, although beneficial, have not been shown to adequately slow the decline in the estimated glomerular filtration rate (eGFR), which increases the risk of kidney failure developing in most patients, within their lifetime.[8-10] Consequently, a disease-modifying therapy capable of stabilizing kidney function over time is an unmet need.

IgA nephropathy is a B-cell–mediated immune complex glomerulonephritis.[1,11-13] Development of IgA nephropathy involves the production of the autoantigen galactose-deficient IgA1, formation of anti–galactose-deficient IgA1 autoantibodies that drive immune-complex formation, immune-complex deposition in the glomerular mesangium, and subsequent inflammation and injury that results in nephron loss.[14] The cytokines B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) bind to the human transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI) receptor on B cells and appear to have key roles in the pathophysiology of IgA nephropathy, including stimulating B-cell and plasma-cell survival and maturation and IgA class switching.[1,11,12,15,16] BAFF and APRIL have been linked to elevated levels of galactose-deficient IgA1, which is considered to lead to the subsequent steps in the pathophysiology of IgA nephropathy that result in disease progression.[11,15,17-19]

Atacicept is a native human TACI–Fc fusion protein with picomolar binding affinity for BAFF and APRIL that modulates B-cell activity, which reduces circulating levels of galactose-deficient IgA1, anti–galactose-deficient IgA1 autoantibodies, and immune complexes.[11,20] The ability of atacicept to decrease BAFF and APRIL signaling of B cells directly targets the upstream pathophysiology of IgA nephropathy.[8-10]

A phase 2b trial (ORIGIN 2b) evaluated the safety and efficacy of atacicept in patients with IgA nephropathy that had been confirmed by biopsy and showed a significant treatment benefit as compared with placebo with respect to the mean percentage change in the 24-hour urinary protein-to-creatinine ratio at 24 weeks (the primary end point). In addition, at 36 weeks, the reduction in the galactose-deficient IgA1 level, resolution of hematuria, and stabilization of the eGFR favored the atacicept group over the placebo group.[21] In an open-label, 60-week extension period, the patients in the atacicept group had further reductions in proteinuria and the level of galactose-deficient IgA1, as well as resolution of hematuria. Through 96 weeks of atacicept treatment, eGFR was stabilized at the mean (±SE) annualized slope of −0.6±0.5 ml per minute per 1.73 m^2 of body-surface area, a rate similar to that in the general population without kidney disease.[21] These results suggest that atacicept may offer a long-term, disease-modifying treatment for IgA nephropathy.[21]

The phase 3 trial (ORIGIN 3), which is evaluating the long-term efficacy and safety of atacicept, a dual BAFF and APRIL inhibitor, over the course of a 2-year period, was designed to enroll a similar patient population and evaluate the same atacicept dose and regimen as in the ORIGIN 2b trial. Here, we report the results from the prespecified 36-week interim analysis.

Methods

Trial Design and Oversight

This international, double-blind, randomized, placebo-controlled phase 3 trial is being conducted in 31 countries across 157 investigative sites to evaluate the safety and efficacy of atacicept, 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). We randomly assigned eligible patients in a 1:1 ratio to receive once-weekly atacicept (at a dose of 150 mg) or matching placebo. Randomization was performed with the use of a centralized, interactive Web-based response system and stratified according to the following prespecified factors: eGFR at screening (<45 ml per minute per 1.73 m^2, ≥45 to <90 ml per minute per 1.73 m^2, or ≥90 ml per minute per 1.73 m^2), total urinary excretion of protein (<2 or ≥2 g per day), use of a stable sodium–glucose cotransporter 2 (SGLT2) inhibitor at screening (yes or no), and geographic region (Asia or any other region). The trial is being overseen by a steering committee of academic leaders,

in partnership with the sponsor (Vera Therapeutics). The sponsor was responsible for the trial design, data collection, and data analysis. The authors vouch for the completeness and accuracy of the data and the fidelity of the trial to the trial protocol, available at NEJM.org. An independent data monitoring committee reviewed the trial data. The first draft of the manuscript was written by the first and last authors, which was revised by the coauthors with medical writing support funded by the sponsor. The authors signed data confidentiality agreements that did not restrict their access to the data. The decision to submit the manuscript for publication was made by all the authors and the sponsor, which retains the data. The trial was approved by the local ethics committees, and it was conducted with written informed consent of the patients, according to the principles of the Declaration of Helsinki.

PATIENTS

Eligible patients were adults 18 years of age or older with IgA nephropathy confirmed by biopsy. Other key inclusion criteria included a 24-hour urinary protein-to-creatinine ratio of at least 1.0 (with protein and creatinine both measured in grams) or proteinuria (defined as a urinary excretion of protein of ≥1.0 g per day), an eGFR of at least 30 ml per minute per 1.73 m^2, treatment with a stable renin–angiotensin system (RAS) inhibitor at the maximum labeled or tolerated dose for at least 12 weeks, and a blood pressure of 150/90 mm Hg or lower. Patients who were undergoing treatment with SGLT2 inhibitors at the time of enrollment had to have been receiving a stable dose for at least 12 weeks before screening and were expected to maintain a stable dose during the trial period. Patients were excluded from the trial if they had IgA nephropathy secondary to another condition, if nephrotic syndrome developed within 6 months before screening, or if evidence of rapidly progressive glomerulonephritis was found. The population in this trial was representative of the general population of patients with IgA nephropathy and was consistent with the patients involved in other IgA nephropathy trials (Table S1).

END POINTS

The primary efficacy end point was the change from baseline at week 36 in the urinary protein-to-creatinine ratio (computed on the natural log scale and derived from a 24-hour urine collection). The secondary end points assessed at the interim analysis at week 36 included the change from baseline in the natural log–transformed serum galactose-deficient IgA1 levels and resolution of hematuria. The results for the secondary end point of the change from baseline in the eGFR at week 52 are not reported in this interim analysis in accordance with guidance from regulatory authorities to sponsors of registrational trials in IgA nephropathy. Exploratory end points at week 36 included the change from baseline in the natural log–transformed urinary albumin-to-creatinine ratio and immunoglobulin biomarkers (IgA, IgG, and IgM). The effect of atacicept will be assessed further at week 104.

STATISTICAL ANALYSIS

For the interim analysis of the primary end point, we calculated that a sample size of 200 patients would provide the trial with 92% power, at a two-sided alpha level of 0.01, to show superiority of atacicept to placebo in reducing the 24-hour urinary protein-to-creatinine ratio. The sample size was based on the assumption that the ratio would be 33% lower in the atacicept group than in the placebo group, with a standard deviation of 0.7 on the natural log scale.

The interim analysis included the first 203 patients who had undergone randomization and had received at least one dose of atacicept or placebo. The change from baseline in the natural log–transformed urinary protein-to-creatinine ratio at week 36 was analyzed with the use of a mixed-effects model for repeated measures (MMRM), with trial group, visit (as a categorical variable), trial-group-by-visit interaction, baseline natural log–transformed urinary protein-to-creatinine ratio, baseline eGFR category, SGLT2 inhibitor use at baseline, and geographic region as fixed effects, with patient as a random effect. The log-transformed change in the urinary protein-to-creatinine ratio from baseline was estimated with the use of least-squares means. To facilitate the interpretation of the result, the least-squares means estimate was back-exponentiated to obtain the equivalent geometric mean percentage change. The MMRM analysis included data obtained from patients in the double-blind period up to week 36, regardless of discontinuation of the trial regimen or initiation of rescue treatment for IgA nephropathy or use of prohib-

ited therapy. Missing values after withdrawal from the trial were imputed with the use of a jump-to-reference (placebo) approach, which was performed 100 times. The results estimated from each of the 100 imputation datasets were combined according to Rubin's rules.[22]

The secondary and exploratory end points evaluated in the interim analysis included all the data from the double-blind period up to week 36, analyzed according to the treatment policy strategy (intention-to-treat principle). For these end points, missing data were handled implicitly by the statistical model. The change from baseline in the natural log–transformed galactose-deficient IgA1 levels, urinary albumin-to-creatinine ratio, and immunoglobulin biomarkers was analyzed with the use of an MMRM similar to that used for the primary end point. The proportion of patients with resolution of hematuria was analyzed with the use of a logistic-regression model for repeated measures. All the repeated-measures models, including the logistic-regression model for hematuria, used an unstructured covariance matrix to account for within-patient correlation. The logistic-regression model included the indicator variable of whether resolution of hematuria was achieved as the dependent variable, and stratification factors, trial group, visit, and trial-group-by-visit interaction as fixed effects. These analyses were not adjusted for multiplicity and should not be used in place of hypothesis testing. The odds ratio for the atacicept treatment effect

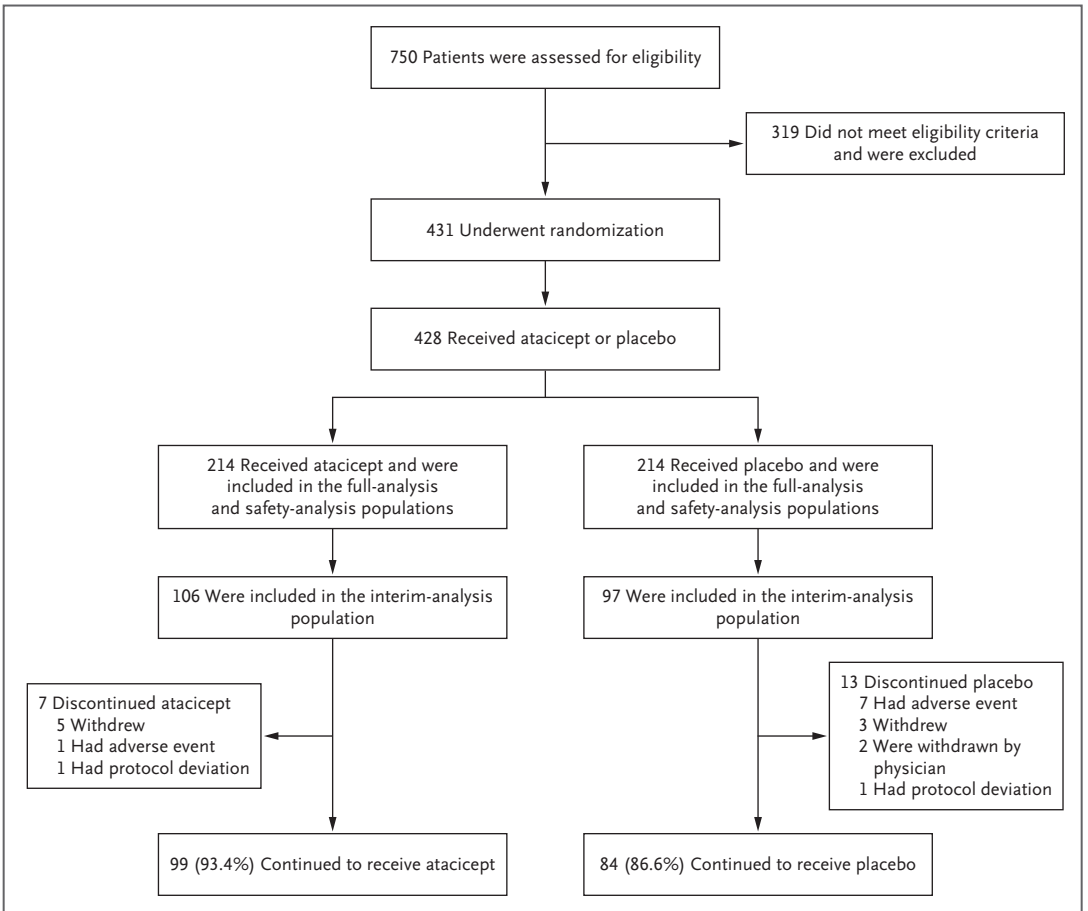


Figure 1. Screening, Randomization, and Follow-up.

Shown are the events that occurred up to the data-cutoff date of May 15, 2025, for the interim analysis. The efficacy analyses included the first 203 patients who had undergone randomization in the main trial population and completed the week 36 visit or had discontinued the trial by week 36. In the interim analysis, 99 patients in the atacicept group and 84 in the placebo group continued the trial regimen after week 36. Safety was assessed in the 428 patients in the main trial population.

at week 36 and corresponding two-sided 95% confidence intervals, along with the change from baseline in the percentage of patients with hematuria at each postbaseline visit up to week 36, are presented.

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 descriptively.

RESULTS

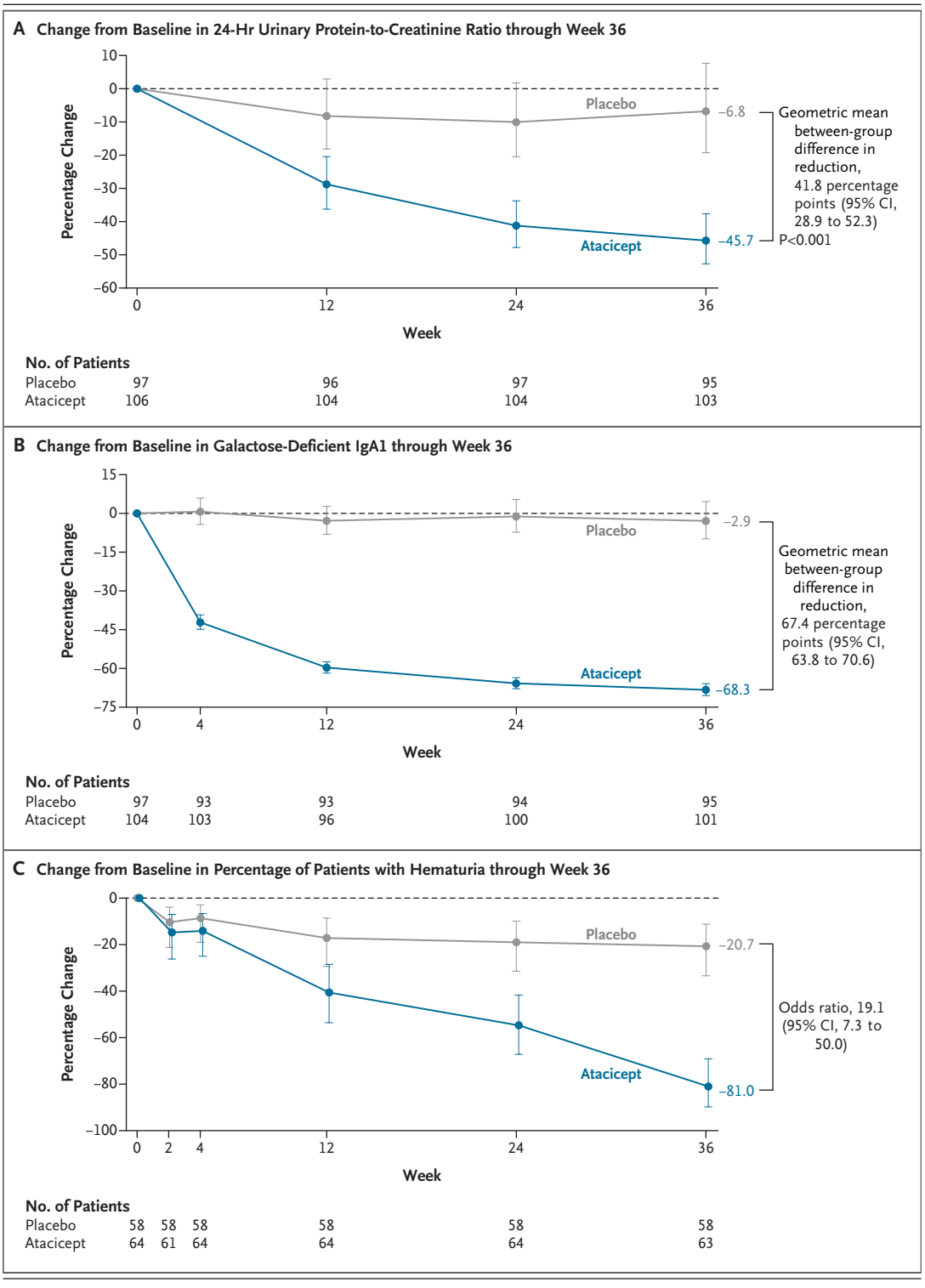
PATIENTS

A total of 203 patients were included in the 36-week interim efficacy analysis; 106 patients were assigned to receive atacicept and 97 to receive placebo. A total of 428 patients (214 in the atacicept group and 214 in the placebo group) were included in the safety analysis (Fig. 1). The demo-

Table 1. Characteristics of the Patients at Baseline (Interim Analysis).*

Characteristic	Atacicept (N=106)	Placebo (N=97)
Age — yr	40.1±11.1	40.9±11.6
Sex — no. (%)		
Male	57 (54)	58 (60)
Female	49 (46)	39 (40)
Race or ethnic group — no. (%)†		
American Indian or Alaska Native	0	0
Asian	59 (56)	52 (54)
Black or African American	0	1 (1)
Native Hawaiian or other Pacific Islander	0	1 (1)
White	46 (43)	42 (43)
Other	1 (1)	1 (1)
Hispanic or Latino	14 (13)	6 (6)
Non-Hispanic or non-Latino	92 (87)	91 (94)
Hematuria — no. (%)‡		
Negative or trace amount of blood	42 (40)	39 (40)
1+	21 (20)	16 (16)
2+	25 (24)	20 (21)
3+	18 (17)	22 (23)
Urinary protein-to-creatinine ratio§	1.7±0.9	1.8±1.2
Estimated glomerular filtration rate — ml/min/1.73 m^2	65.3±27.7	64.9±29.0
Urinary protein excretion — g/day	2.2±1.0	2.3±1.4
Urinary albumin-to-creatinine ratio§	1.3±0.7	1.3±0.9
Galactose-deficient IgA1 — μg/liter	5248.2±4192.5	4671.8±2411.7
IgA — mg/dl	336.7±119.1	332.5±109.8
IgG — mg/dl	1165.9±278.7	1150.1±277.0
IgM — mg/dl	111.8±57.1	99.1±54.8
Stable use of SGLT2 inhibitor — no. (%)	59 (56)	49 (51)
Use of RAS inhibitor — no. (%)	105 (99)	97 (100)
Time since biopsy — yr	2.5±2.6	2.5±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. "Other" includes patients with multiple races.
‡ Hematuria was defined by a dipstick reading of more than 1+.
§ For these measures, protein, albumin, and creatinine were measured in grams.



graphic and clinical characteristics of the patients were similar in the two groups (Table 1). At baseline, 99.5% of the patients in the interim analysis (202 of 203) were receiving a maximum labeled or maximum tolerated stable dose of an RAS inhibitor, and 53.2% of the patients (108 patients; 59 in the atacicept group and 49 in the placebo group) were receiving a stable dose of an SGLT2 inhibitor.

Figure 2 (facing page). Percentage Change in Urinary Protein-to-Creatinine Ratio, Galactose-Deficient IgA1 Level, and Hematuria.

Panel A shows the mean percentage change from baseline through week 36 in the 24-hour urinary protein-to-creatinine ratio (primary end point). At week 36, data were available for 103 patients in the atacicept group and 95 patients in the placebo group. Panel B shows the mean percentage change from baseline through week 36 in the galactose-deficient IgA1 level. Panel C shows the change from baseline through week 36 in the percentage of patients with hematuria; the number of patients at each visit is the number of patients with baseline hematuria (≥1+), determined on the basis of dipstick testing, and nonmissing values. I bars indicate 95% confidence intervals. The between-group difference in the geometric mean percentage reduction in the 24-hour urinary protein-to-creatinine ratio at week 36 was calculated as $[1-(1-0.457)\div(1-0.068)]\times 100=41.8\%$, which represents the atacicept treatment effect; the between-group difference in the geometric mean percentage reduction in the galactose-deficient IgA1 level at week 36 was computed with the use of the same method. The 95% confidence intervals for the percentage of patients with hematuria at each postbaseline visit were computed with the use of the Clopper–Pearson method. The analyses of the galactose-deficient IgA1 level and percentage of patients with hematuria were not adjusted for multiplicity and should not be used in place of hypothesis testing.

EFFICACY

At week 36, the percentage reduction from baseline in the 24-hour urinary protein-to-creatinine ratio was 45.7% in the atacicept group and 6.8% in the placebo group (Fig. 2A). These findings correspond to a geometric mean between-group difference of 41.8 percentage points (95% confidence interval [CI], 28.9 to 52.3; P<0.001), which indicates a significant reduction in proteinuria favoring atacicept. Proteinuria appeared to decrease as early as week 12, with apparent sustained improvement through week 36 in the atacicept group. Figure 3 shows prespecified subgroup analyses of the 24-hour urinary protein-to-creatinine ratio according to age, sex, region, race, baseline urinary protein-to-creatinine ratio, baseline eGFR, and baseline SGLT2 inhibitor use.

At week 36, the reduction from baseline in the galactose-deficient IgA1 level was 68.3% in the atacicept group and 2.9% in the placebo group (Fig. 2B). The reductions in the galactose-deficient IgA1 level appeared as early as week 4. At week 36, among the 122 patients (60.1% of the 203 patients included in the interim analysis) with baseline hematuria (≥1+) determined on the basis of dipstick testing, resolution of hematuria (defined as a reduction to negative or trace dipstick findings) had occurred in 51 of 63 patients (81.0%) in the atacicept group and in 12 of 58 (20.7%) in the placebo group (Fig. 2C). The reduction from baseline in the urinary albumin-to-creatinine ratio was 47.3% in the atacicept group and 8.8% in the placebo group (Fig. S2).

SAFETY

The safety analysis included all the patients who had undergone randomization and had received at least one dose of atacicept or placebo (214 in each group). The median exposure to atacicept was 34 weeks (range, 2 to 94), and the median exposure to placebo was 31 weeks (range, 1 to 81). Adverse events were reported in 127 of 214 patients (59.3%) in the atacicept group and in 107 of 214 (50.0%) in the placebo group (Table 2). Injection-site reactions were reported in 19.2% of the patients in the atacicept group and in 1.9% of those in the placebo group, most of which were mild in severity. Serious adverse events occurred in 1 patient (0.5%) in the atacicept group and in 11 patients (5.1%) in the placebo group. The single serious adverse event in the atacicept group, involving cholecystitis, was considered by the site investigator to be unrelated to the trial drug. No deaths occurred.

The incidence rate of infection was similar in the atacicept and placebo groups. Serious adverse events related to infection or infestation occurred in 3 patients in the placebo group and in no patients in the atacicept group. No opportunistic infections were reported.

Serum levels of IgG, IgA, and IgM decreased as expected after treatment with atacicept, which is consistent with its mechanism of action owing to B-cell modulation. The decreased immunoglobulin levels stabilized after week 24 (Fig. S3). No occurrences of hypogammaglobulinemia, or associated clinical symptoms, were reported. Hypersensitivity reactions were reported in 8 patients (3.7%) in the atacicept group and in 14 patients (6.5%) in the placebo group.

DISCUSSION

In the ORIGIN 3 trial, the participants were representative of the general population of patients with IgA nephropathy and persistent proteinuria

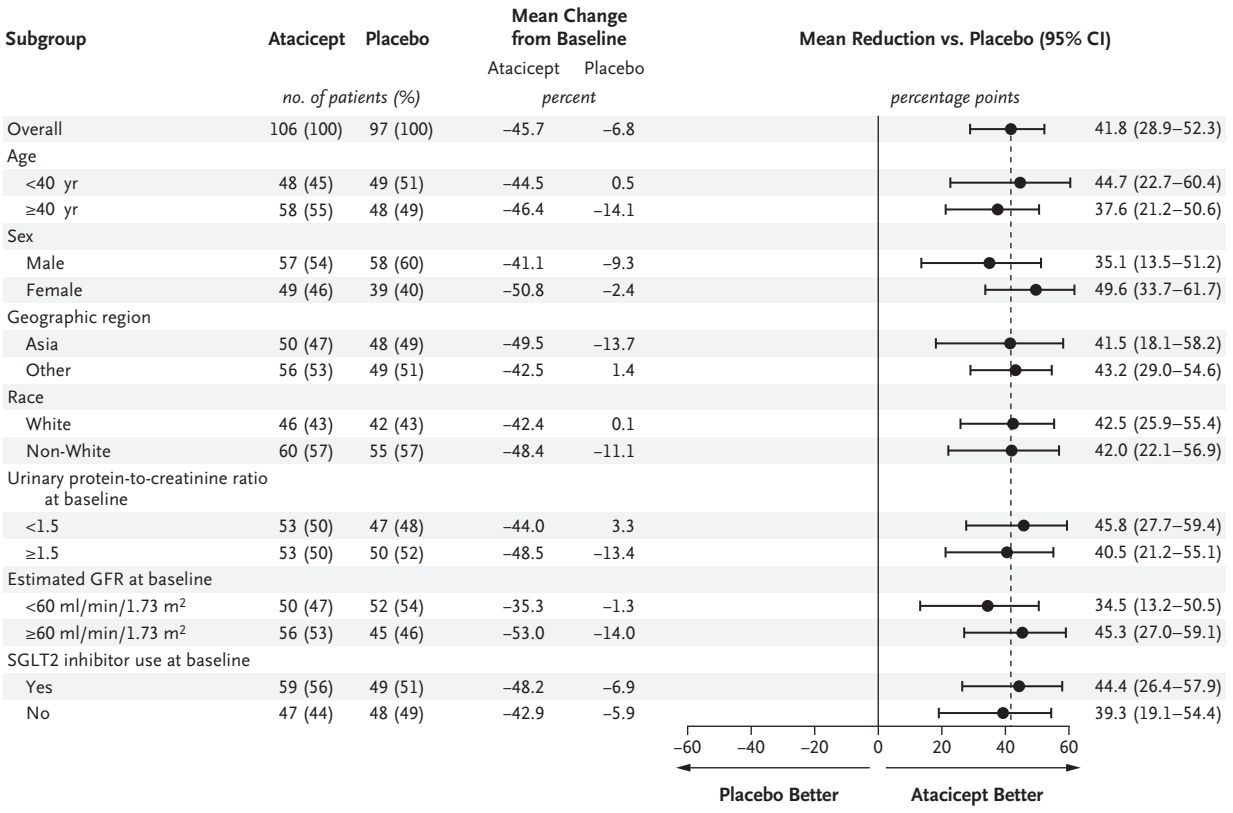


Figure 3. Subgroup Analyses of the Primary End Point.

Shown are prespecified subgroup analyses of the mean percentage change from baseline at week 36 in the 24-hour urinary protein-to-creatinine ratio. Separate analyses were conducted for each subgroup category with the use of the same imputed datasets and the same mixed-effects model with repeated measures (MMRM) model as for the primary analysis. If the subgroup was one of the covariates in the model, the covariate was removed from the model statement when the model was used for the particular subgroup. The number of patients per subgroup represents the sample size of the subgroup. The percentage of patients represents the number of patients per subgroup divided by the overall number of patients per trial group included in the analysis (patients with nonmissing baseline data and nonmissing covariates). The analyses were not adjusted for multiplicity and should not be used in place of hypothesis testing. The urinary protein-to-creatinine ratio was calculated with protein and creatinine both measured in grams. GFR denotes glomerular filtration rate, and SGLT2i sodium–glucose cotransporter 2 inhibitor.

despite appropriate standard care, including treatment with RAS inhibitors and, in many cases, SGLT2 inhibitors. Such patients are considered to be at high risk for progressive loss of kidney function and kidney failure, despite the available treatment options. Treatment with atacicept resulted in a significantly greater reduction in the urinary protein-to-creatinine ratio (the primary end point) than placebo. Treatment with atacicept was also associated with reductions in the galactose-deficient IgA1 level and resolution of hematuria. These findings confirm the results of the phase 2b trial, which enrolled a similar patient population and used the same atacicept dose and regimen. The previous phase 2b trial also showed that atacicept reduced proteinuria, and results for the secondary end points evaluating the change from baseline in the galactose-deficient IgA1 level and resolution of hematuria were consistent in the two trials. In the phase 2b study, atacicept was associated with stabilizing the eGFR over the course of 96 weeks of treatment.[11] The consistency of these findings in both trials suggests that dual BAFF and APRIL inhibition with atacicept may modify the disease course, presumably by targeting the underlying pathophysiology of IgA nephropathy.

Proteinuria is a validated surrogate end point for kidney outcomes in patients with IgA nephropathy, and a reduction in proteinuria has generally

Table 2. Adverse Events (Safety Analysis).*

Event	Atacicept (N=214)	Placebo (N=214)
	no. of patients (%)	
Any adverse event	127 (59.3)	107 (50.0)
Mild	90 (42.1)	74 (34.6)
Moderate	34 (15.9)	24 (11.2)
Severe	3 (1.4)	9 (4.2)
Adverse events occurring in >5% of the patients in either group		
Injection-site reaction	41 (19.2)	4 (1.9)
Upper respiratory tract infection	26 (12.1)	19 (8.9)
Nasopharyngitis	17 (7.9)	13 (6.1)
Injection-site erythema	12 (5.6)	1 (0.5)
Any adverse event related to the trial regimen	63 (29.4)	22 (10.3)
Mild	55 (25.7)	15 (7.0)
Moderate	8 (3.7)	5 (2.3)
Severe	0	2 (0.9)
Any serious adverse event	1 (0.5)†	11 (5.1)
Any adverse event related to infection or infestation	68 (31.8)	60 (28.0)
Mild	55 (25.7)	48 (22.4)
Moderate	13 (6.1)	10 (4.7)
Severe	0	2 (0.9)
Any serious adverse event related to infection or infestation	0	3 (1.4)
Any adverse event associated with injection-site reactions‡	62 (29.0)	11 (5.1)
Mild	56 (26.2)	10 (4.7)
Moderate	6 (2.8)	1 (0.5)
Severe	0	0
Any adverse event related to the trial regimen and associated with injection-site reactions	51 (23.8)	11 (5.1)
Any adverse event leading to interruption of the trial regimen	5 (2.3)	5 (2.3)
Any adverse event leading to discontinuation of the trial regimen	2 (0.9)	8 (3.7)
Any adverse event leading to death	0	0

* The safety analyses included all the patients who underwent randomization and received at least one dose of atacicept or placebo. Safety data were summarized with the use of descriptive statistics.
† The single serious adverse event in the atacicept group, involving cholecystitis, was determined by the site investigator to be unrelated to treatment.
‡ Adverse events associated with injection-site reactions included 17 prespecified preferred terms under the high-level term of "injection-site reactions," reported in the *Medical Dictionary for Regulatory Activities* (MedDRA), version 27.1.

been associated with slowing the decline in kidney function.[4,13,23,24] In the ORIGIN 3 trial, atacicept treatment resulted in a 45.7% reduction in the urinary protein-to-creatinine ratio from baseline, as compared with a 6.8% reduction in the placebo group. The between-group difference of 41.8 percentage points in the reduction from baseline in the urinary protein-to-creatinine ratio was significant and considered clinically meaningful. This large effect on proteinuria remained consistent across prespecified subgroups.

Analyses of secondary end points showed decreases in other markers of disease activity, such as reductions in the level of galactose-deficient IgA1.[25,26] Hematuria, a hallmark of glomerular inflammation in IgA nephropathy, was also re-

duced. Reduced levels of galactose-deficient IgA1, associated autoantibodies, and circulating immune complexes among participants treated with atacicept suggest that this therapy may help mitigate the glomerular injury that gives rise to hematuria.[27] The decrease in the level of galactose-deficient IgA1 occurred very early in the trial, at 4 weeks, preceding the proteinuria reduction at 12 weeks, which supports the idea that treatment with atacicept early in the disease course of IgA nephropathy may result in downstream clinical benefits. The observed temporal pattern of improvement in both hematuria and proteinuria suggests that atacicept may have antiinflammatory activity similar to that of systemic glucocorticoids and complement inhibitors.[11] We postulate that this therapeutic effect is driven by a rapid reduction in pathogenic immune complexes and may be further supported by the modulation of innate immune responses through BAFF and APRIL blockade, given that cells such as macrophages also express TACI.[28]

The safety profile of atacicept observed in this trial was consistent with the results of previous trials of atacicept in patients with IgA nephropathy.[11,21] Most adverse events were mild or moderate in severity. The percentage of patients with serious adverse events was 0.5% in the atacicept group and 5.1% in the placebo group, and no deaths occurred in either group.

The effects of treatment with atacicept appeared to occur without evidence of B-cell depletion or immunosuppressive effects, which is similar to the safety results observed through 96 weeks in the ORIGIN 2b trial.[21] In the present trial, atacicept led to expected reductions in serum immunoglobulin levels, but no increased risk of infection with exposure was observed for up to 94 weeks. Across both the phase 3 and phase 2b trials of atacicept, a similar incidence of infection was observed in the atacicept and placebo groups, with no reported cases of opportunistic infections, hypogammaglobulinemia, or demyelinating events. Atacicept has been shown to act upstream by selectively inhibiting the B-cell survival factors BAFF and APRIL, which decreases pathogenic antibody production while maintaining immunoglobulin levels that preserve immune competence.[11,20]

The strengths of this trial include its placebo-controlled design, international site participation, high adherence to the trial protocol, and the requirement that patients had to be receiving appropriate standard treatment at a stable dose for their IgA nephropathy. In addition, 53.2% of the patients were receiving stable doses of SGLT2 inhibitors, a drug class that is increasingly part of standard care for chronic kidney disease.[29] Despite the difficulties often associated with 24-hour urine collection at multiple visits, the accepted standard test for proteinuria, the 24-hour urine sample was missing for only 5 of 203 patients (2.5%) at week 36, which led to the determination that the findings for the primary end point were robust. Lastly, the participating sites generated equal representation from Asian and non-Asian regions, which enables applicability across the populations most affected by IgA nephropathy.

This interim report has certain limitations. It does not include a description of the effect of atacicept on eGFR; these results have not yet been disclosed because the blinded portion of this trial is ongoing. The previous long-term results showed that eGFR stabilized over the course of 96 weeks of atacicept treatment to a rate of decline similar to that observed in the general population without kidney disease.[21] The ongoing trial is designed to assess the long-term benefits of atacicept as a targeted, disease-modifying therapy that stabilizes kidney function.

This prespecified interim analysis showed that among patients with IgA nephropathy, treatment with atacicept resulted in a significantly greater reduction in proteinuria than placebo at week 36.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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

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