ORIGINAL ARTICLE

Atrasentan in Patients with IgA Nephropathy

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ABSTRACT

BACKGROUND

Patients with IgA nephropathy and severe proteinuria have a high lifetime risk of kidney failure. The efficacy and safety of the selective endothelin type A receptor antagonist atrasentan in reducing proteinuria in patients with IgA nephropathy are incompletely understood.

METHODS

We are conducting a phase 3, multinational, double-blind, randomized, controlled trial involving adults with biopsy-proven IgA nephropathy, a total urinary protein excretion of at least 1 g per day, and an estimated glomerular filtration rate of at least 30 ml per minute per 1.73 m^2 of body-surface area. Patients were randomly assigned to receive atrasentan (0.75 mg per day) or matched placebo for 132 weeks. The primary outcome, assessed at a prespecified interim analysis of data from the first 270 patients in the main stratum, was the change in the 24-hour urinary protein-to-creatinine ratio from baseline to week 36; the change was estimated with the use of a repeated-measures model. (An exploratory stratum of patients who were receiving a sodium–glucose cotransporter 2 inhibitor were included in a separate analysis.) Safety analyses were based on adverse events across the entire main stratum.

RESULTS

A total of 340 patients were recruited into the main stratum. Among the first 270 patients in the main stratum (135 per trial group) who completed the week 36 visit, the geometric mean percentage change in the urinary protein-to-creatinine ratio relative to baseline was significantly greater with atrasentan (–38.1%) than with placebo (–3.1%), with a geometric mean between-group difference of –36.1 percentage points (95% confidence interval, –44.6 to –26.4; P<0.001). The percentage of patients with adverse events did not differ substantially between the two groups. Fluid retention was reported by 19 of 169 patients (11.2%) in the atrasentan group and in 14 of 170 (8.2%) in the placebo group but did not lead to discontinuation of the trial regimen. No apparent cases of cardiac failure or severe edema occurred.

CONCLUSIONS

In this prespecified interim analysis, atrasentan resulted in a significant and clinically meaningful reduction in proteinuria as compared with placebo in patients with IgA nephropathy. (Funded by Novartis; ALIGN ClinicalTrials.gov number, NCT04573478.)

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*A complete list of the ALIGN Study Investigators is available in the Supplementary Appendix, available at NEJM.org.

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IgA nephropathy is the most common primary glomerular disease in the world and is associated with a substantial lifetime risk of kidney failure.[1,2] Current guideline-recommended treatment of IgA nephropathy is focused on reducing proteinuria and slowing progressive loss of kidney function with nonimmunosuppressive therapies, including lifestyle modification and renin–angiotensin system (RAS) inhibition.[3] However, despite these treatments, the risk of kidney failure remains high, which highlights the need for new therapies that target different aspects of the disease pathophysiology.

Endothelin-1 is a vasoactive peptide implicated in the pathophysiology of IgA nephropathy. Binding of endothelin-1 to the endothelin type A receptor in the kidney causes endothelial and podocyte damage, mesangial expansion, and tubular inflammation in experimental models of IgA nephropathy.[4,5] Atrasentan, a selective inhibitor of the endothelin type A receptor, exerts antiproliferative, antifibrotic, and antiinflammatory effects in experimental models of IgA nephropathy.[6,7] In the IgA nephropathy stratum of the open-label AFFINITY basket trial, the addition of atrasentan to maximum tolerated doses of angiotensin-converting–enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) reduced the 24-hour urinary protein-to-creatinine ratio by 48% after 12 weeks of treatment.[8] Moreover, among patients with type 2 diabetes and chronic kidney disease, atrasentan reduced the risk of

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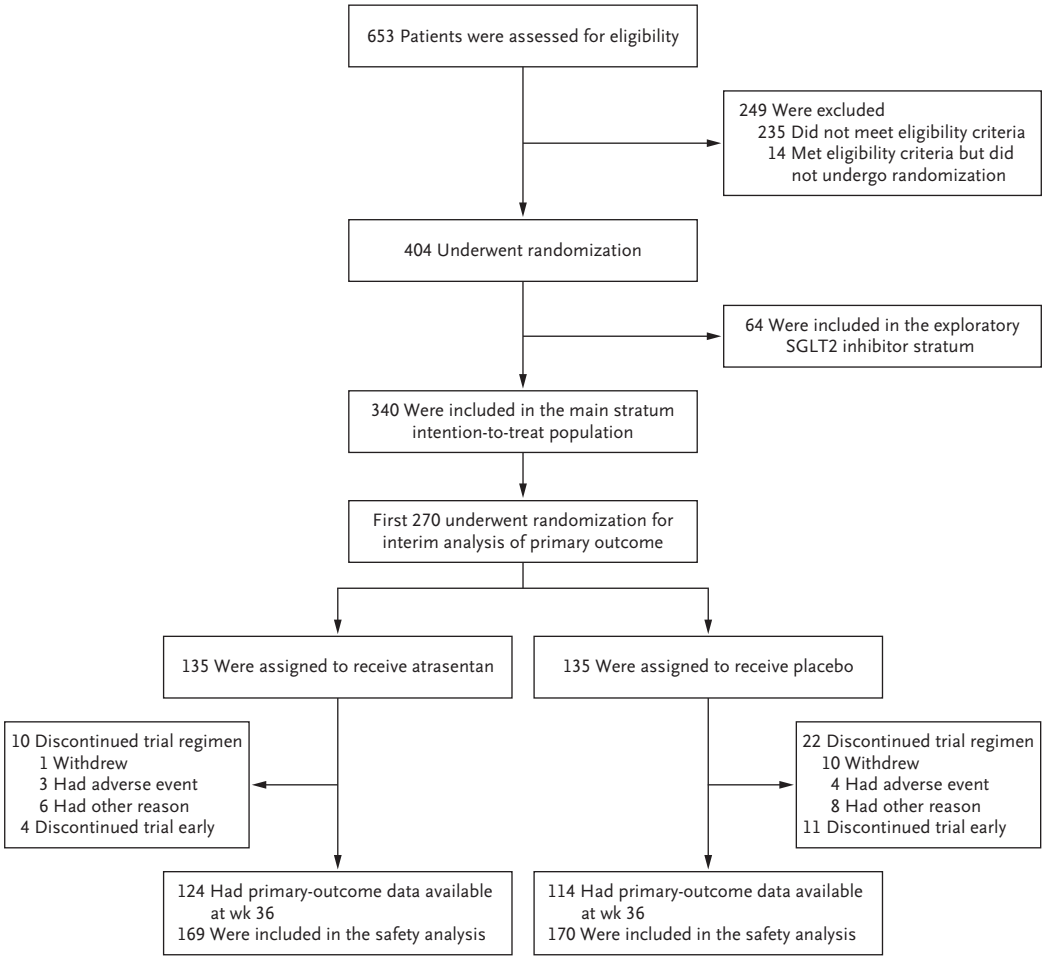


Figure 1. Screening, Randomization, and Follow-up.
SGLT2 denotes sodium–glucose cotransporter 2.

Table 1. Demographic and Clinical Characteristics of the First 270 Patients in the Main Stratum.*

Characteristic	Atrasentan (N=135)	Placebo (N=135)
Age — yr	45.7±12.9	44.1±11.0
Female sex — no. (%)	54 (40.0)	57 (42.2)
Race — no. (%)†		
Asian	75 (55.6)	79 (58.5)
White	49 (36.3)	48 (35.6)
Black	4 (3.0)	1 (0.7)
Other	7 (5.2)	7 (5.2)
Geographic region		
Asia	64 (47.4)	63 (46.7)
Latin America and the Caribbean	29 (21.5)	23 (17.0)
Northern America: Canada and United States	20 (14.8)	26 (19.3)
Europe	11 (8.1)	13 (9.6)
Oceania	11 (8.1)	10 (7.4)
Body-mass index‡	27.05±5.44	27.66±6.46
Duration of disease — yr	5.14±5.41	6.14±6.04
Blood pressure — mm Hg		
Systolic	125.4±13.3	122.9±12.3
Diastolic	79.6±9.8	78.7±9.0
Median total urinary protein excretion (IQR) — mg/day	1847.4 (1314.0–2775.9)	1851.0 (1328.9–2550.0)
24-Hour urinary protein-to-creatinine ratio§		
Median (IQR)	1435.7 (1006.7–1988.6)	1429.2 (1100.9–1918.3)
Distribution — no. (%)		
<1500	72 (53.3)	76 (56.3)
≥1500	63 (46.7)	59 (43.7)
Median 24-hour urinary albumin-to-creatinine ratio (IQR)¶	1051.3 (769.2–1485.8)	1059.3 (770.2–1480.8)
Estimated glomerular filtration rate		
Mean — ml/min/1.73 m^2	58.28±23.75	59.49±24.42
Distribution — no. (%)		
≤45 ml/min/1.73 m^2	54 (40.0)	53 (39.3)
>45–60 ml/min/1.73 m^2	25 (18.5)	28 (20.7)
>60 ml/min/1.73 m^2	56 (41.5)	54 (40.0)
Hemoglobin level — g/dl	13.58±1.73	13.70±1.74
Use of RAS inhibitor at baseline — no. (%)		
ARB only	97 (71.9)	95 (70.4)
ACE inhibitor only	37 (27.4)	37 (27.4)
Use of diuretic at baseline — no./total no. (%)	21/134 (15.7)‖	16/135 (11.9)

* Plus–minus values are means ±SD. A total of 340 patients were recruited into the main stratum; shown are the characteristics of the first 270 patients who completed the week 36 visit (intention-to-treat population). Atrasentan was administered at a dose of 0.75 mg per day. Percentages may not total 100 because of rounding. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, IQR interquartile range, and RAS renin–angiotensin system.
† Race was reported by the patients. "Other" includes patients with multiple races and no races reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Urinary protein was measured in milligrams, and urinary creatinine was measured in grams.
¶ Urinary albumin was measured in milligrams, and urinary creatinine was measured in grams.
‖ The percentage was calculated on the basis of the safety population.

a composite of doubling of the serum creatinine level or kidney failure by 35%.[9]

Here we present the results of a prespecified analysis of the ALIGN trial, which is assessing the efficacy and safety of atrasentan as compared with placebo in reducing proteinuria and the decline in the estimated glomerular filtration rate (eGFR) in patients with IgA nephropathy.

METHODS

TRIAL DESIGN AND OVERSIGHT

The design of this phase 3, multinational, double-blind, randomized, placebo-controlled trial has been published[10] and is summarized in Figure S1 in the Supplementary Appendix, available with full text of this article at NEJM.org. The trial was sponsored by Novartis. A steering committee of eight academic members and three sponsor employees was responsible for the design and oversight of the trial and reporting of the results. The trial protocol (available at NEJM.org) was approved by a central or local ethics committee at each trial site, and the statistical analysis plan is available with the protocol. All the patients provided written informed consent. The interim analysis was conducted by the sponsor. The first draft of the manuscript was written by the first and last authors and revised by the coauthors. Technical editorial assistance was provided by the sponsor. The authors had access to the full data set and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. The decision to submit the manuscript for publication was made jointly by all the authors.

PATIENTS

Adults (≥18 years of age) with biopsy-proven IgA nephropathy, a total urinary protein excretion of at least 1 g per day, and an eGFR of at least 30 ml per minute per 1.73 m^2 of body-surface area were eligible for participation. Treatment with a maximum tolerated dose of an ACE inhibitor or ARB at a stable dose for at least 12 weeks before screening was required. Patients who were unable to take RAS inhibitors were eligible; however, the

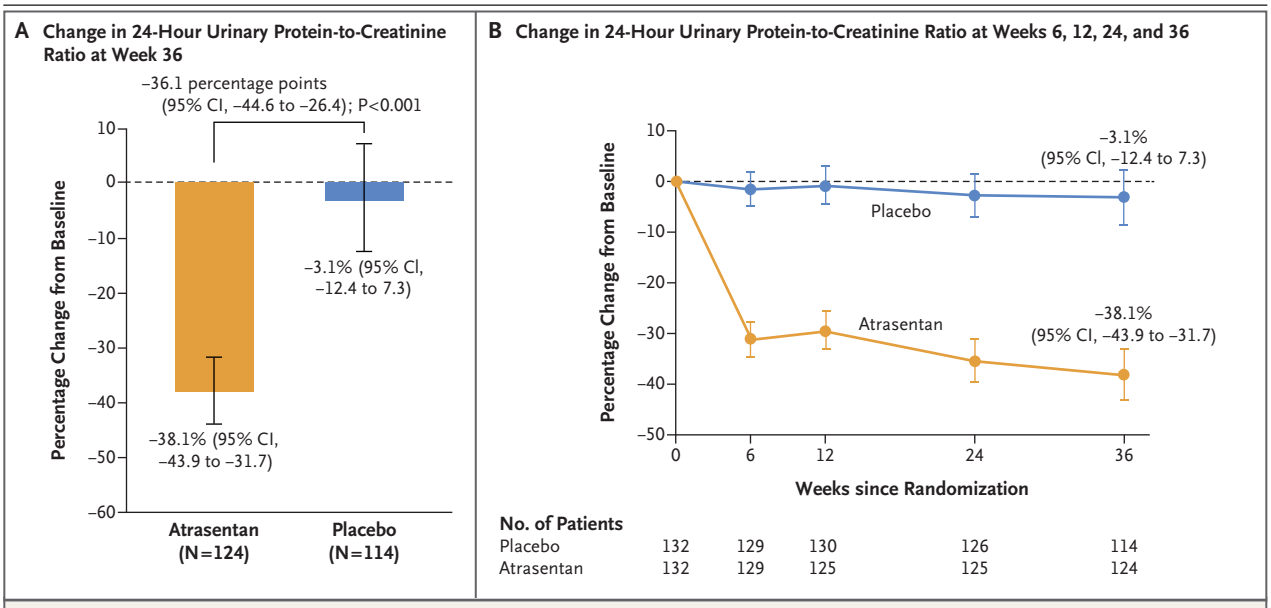
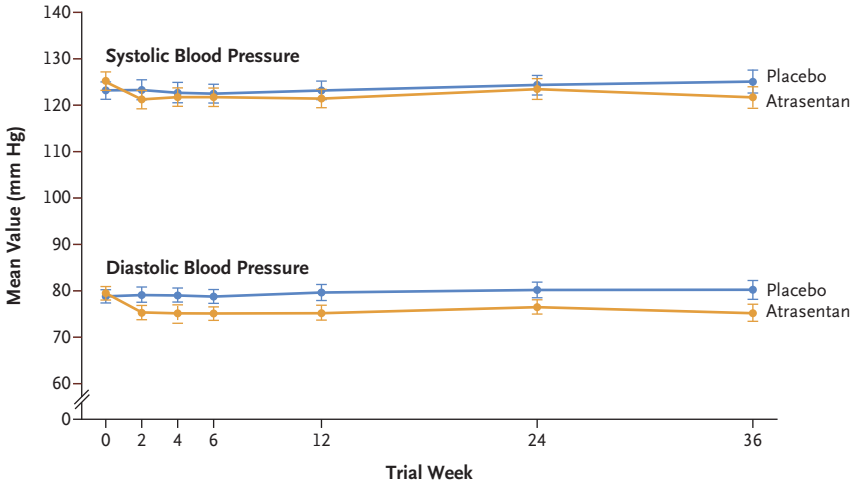


Figure 2. Change in 24-Hour Urinary Protein-to-Creatinine Ratio (Primary Outcome).

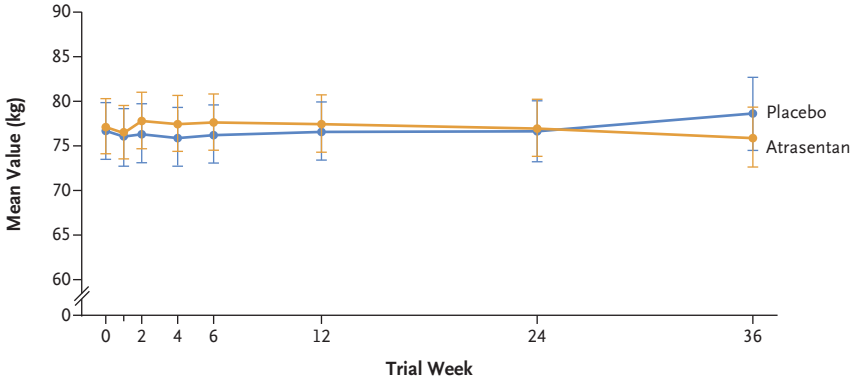
The primary outcome was the change in the 24-hour urinary protein-to-creatinine ratio from baseline to week 36. The prespecified interim analysis involved the first 270 patients in the main stratum (135 patients in each group). Data on the urinary protein-to-creatinine ratio at week 36 were available for 124 patients in the atrasentan group and 114 patients in the placebo group. Panel A shows the geometric least-squares mean percentage change from baseline in the urinary protein-to-creatinine ratio at week 36 as well as the geometric least-squares mean between-group difference. Panel B shows the geometric least-squares mean percentage change in the urinary protein-to-creatinine ratio from baseline at weeks 6, 12, 24, and 36. A total of 3 patients in each group had no postbaseline data for the urinary protein-to-creatinine ratio; these patients were excluded from the number of patients at baseline. I bars indicate 95% confidence intervals in Panel A and standard errors in Panel B.

A Change in Systolic and Diastolic Blood Pressure



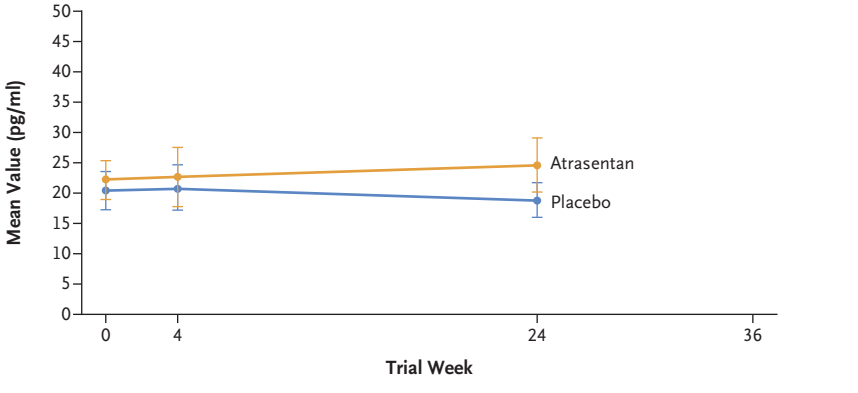
No. of Patients							
Placebo	170	165	161	167	166	157	123
Atrasentan	169	162	164	165	161	154	129

B Change in Body Weight



No. of Patients							
Placebo	170	165	161	167	166	156	123
Atrasentan	169	162	164	165	161	154	129

C Change in B-Type Natriuretic Peptide Level



No. of Patients				
Placebo	170	155	152	
Atrasentan	169	156	151	

Figure 3 (facing page). Blood Pressure, Body Weight, and B-Type Natriuretic Peptide Levels.

Shown are mean values from baseline to week 36 in systolic and diastolic blood pressure (Panel A) and body weight (Panel B) and the mean value from baseline to week 24 in B-type natriuretic peptide (Panel C) in the main stratum of the trial. Laboratory reference ranges for B-type natriuretic peptide according to age are as follows: 0 to 44 years, 2.7 to 33.3 pg per milliliter; 45 to 54 years, 2.7 to 46.7 pg per milliliter; 55 to 64 years, 2.7 to 53.2 pg per milliliter; 65 to 74 years, 2.7 to 72.3 pg per milliliter; and older than 74 years, 2.7 to 176 pg per milliliter. I bars indicate 95% confidence intervals.

total percentage of such patients could not exceed 5% of the total population. Key exclusion criteria were secondary IgA nephropathy, a documented diagnosis of heart failure or previous hospitalization for heart failure, or a B-type natriuretic peptide (BNP) level of more than 200 pg per milliliter. Patients who were receiving a stable dose of a sodium–glucose cotransporter 2 (SGLT2) inhibitor could be enrolled in an exploratory SGLT2 inhibitor stratum in regions where SGLT2 inhibitors were available and approved. This exploratory SGLT2 inhibitor stratum was independent of the main stratum. Full inclusion and exclusion criteria and details of both the main and SGLT2 inhibitor strata are described in the Supplementary Appendix.

TRIAL PROCEDURES

Eligible patients were randomly assigned, in a 1:1 ratio, to receive either atrasentan (0.75 mg once daily) or matching placebo. Randomization was performed with the use of a central interactive Web-based response system and was stratified according to geographic region (Asia vs. all other regions) and urinary protein-to-creatinine ratio (with protein measured in milligrams and creatinine measured in grams) at screening (≥2000 vs. <2000). All parties who are involved in the conduct of the trial remain unaware of the trial-group assignments, with the exception of the data and safety monitoring board and the team responsible for the conduct of the prespecified interim analysis; members of this team were precluded from further participation in any trial-related activity after receiving access to unblinded data.

In-person trial visits were performed at screening, baseline (day 1), and weeks 2, 4, 6, and 12, then every 12 weeks thereafter (such visits will continue until week 132). After the week 132 visit, atrasentan or placebo will be discontinued and the patients will proceed to a 4-week washout period. At all in-person trial visits, blood was drawn for clinical chemical assessment. Twenty-four hour urine samples for assessment of the urinary protein-to-creatinine ratio and urinary albumin-to-creatinine ratio were collected at baseline and at weeks 6, 12, 24, and 36. In addition, first-morning void urine samples for assessment of the urinary protein-to-creatinine ratio and urinary albumin-to-creatinine ratio and vital-sign measurements were collected throughout the trial. Proteinuria and clinical chemical measurements, including the serum creatinine level, were performed in a central laboratory. The eGFR was calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.[11]

OUTCOMES

The primary outcome to evaluate the efficacy of atrasentan was the change in the urinary protein-to-creatinine ratio (based on 24-hour urine collection) from baseline to week 36 after the first 270 patients in the main stratum had undergone the week 36 visit. The exploratory outcome of the change in the urinary protein-to-creatinine ratio from baseline to week 36 in the SGLT2 inhibitor stratum was also examined.

Safety outcomes were any adverse events that emerged or worsened in severity after the initiation of atrasentan or placebo, serious or severe adverse events, and adverse events that led to discontinuation of atrasentan or placebo. These outcomes were assessed in the entire main stratum, not just the first 270 patients. Adverse events were coded according to the *Medical Dictionary for Regulatory Activities* (version 24.0). Because endothelin-receptor antagonists may cause sodium and fluid retention, adverse events of special interest, identified with the use of Food and Drug Administration Medical Query categories, included anemia, vasodilatation, hypotension, cardiac failure, and fluid retention.

STATISTICAL ANALYSIS

The sample-size calculation indicated that 270 patients in the main stratum would provide approximately 90% power with a two-sided alpha

Table 2. Adverse Events in the Main Stratum.*

Event	Atrasentan (N=169)	Placebo (N=170)
	no. of patients (%)	
Any adverse event	139 (82.2)	144 (84.7)
Adverse events occurring in >5% of the patients in either group		
Covid-19	35 (20.7)	37 (21.8)
Nasopharyngitis	17 (10.1)	10 (5.9)
Peripheral edema	15 (8.9)	11 (6.5)
Anemia	11 (6.5)	2 (1.2)
Pyrexia	11 (6.5)	7 (4.1)
Upper respiratory tract infection	11 (6.5)	9 (5.3)
Headache	10 (5.9)	11 (6.5)
Muscle spasms	10 (5.9)	4 (2.4)
Cough	9 (5.3)	4 (2.4)
Diarrhea	9 (5.3)	7 (4.1)
Dizziness	9 (5.3)	6 (3.5)
Hypotension	9 (5.3)	6 (3.5)
Nausea	9 (5.3)	7 (4.1)
Back pain	8 (4.7)	15 (8.8)
Influenza	6 (3.6)	10 (5.9)
Hypertension	2 (1.2)	12 (7.1)
Any serious adverse event	10 (5.9)	11 (6.5)
Any severe adverse event	12 (7.1)	10 (5.9)
Any adverse event leading to discontinuation of atrasentan or placebo	6 (3.6)	6 (3.5)
Adverse event of special interest†		
Anemia‡	14 (8.3)	4 (2.4)
Cardiac failure	0	0
Fluid retention	19 (11.2)	14 (8.2)
Vasodilatation or hypotension	10 (5.9)	7 (4.1)
Any adverse event of special interest	38 (22.5)	24 (14.1)
Any serious adverse event of special interest	0	0
Any moderate or severe adverse event of special interest	10 (5.9)	11 (6.5)
Any adverse event of special interest leading to discontinuation of atrasentan or placebo	0	0

* Shown are adverse events that emerged or worsened in severity after the initiation of atrasentan or placebo. Covid-19 denotes coronavirus disease 2019.
† Adverse events of special interest are shown according to Food and Drug Administration Medical Query category.
‡ No patient with anemia received a blood transfusion.

of 0.01 to detect that the mean percentage change in the urinary protein-to-creatinine ratio from baseline to week 36 was lower by at least 28 percentage points in the atrasentan group than in the placebo group (i.e., a natural log–transformed treatment effect of 0.33), under the assumption of a standard deviation of 0.67 in the log-transformed urinary protein-to-creatinine ratio and a 5% incidence of early discontinuation of the trial before week 36. The primary analysis was conducted after 270 patients in the main stratum of the intention-to-treat population had either

completed the week 36 visit or discontinued the trial. The baseline value for urinary protein-to-creatinine ratio (on a natural log scale) was defined as the mean of the two separate ratio results from 24-hour urine samples collected within 21 days of each other and before the first dose of atrasentan or placebo. If one of the 24-hour urine samples that was collected for the baseline assessment was missing, the single value for 24-hour urinary protein-to-creatinine ratio was used for the baseline assessment.

The primary outcome was the change in the 24-hour urinary protein-to-creatinine ratio from baseline to week 36. The analysis of the primary outcome used a repeated-measures model. The model included the change from baseline in the natural log of the urinary protein-to-creatinine ratio at each postbaseline measurement through week 36 as outcomes. The model also included the fixed effects of trial group, visit, and interaction between trial group and visit, with covariates of the baseline natural log of the urinary protein-to-creatinine ratio and baseline eGFR as continuous variables and the randomization stratification factor of geographic region (Asia vs. all other regions). The covariance structure was assumed to be unstructured and the same in each trial group. 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 percent change. Missing data were assumed to be missing at random. Data on the urinary protein-to-creatinine ratio that were collected after an intercurrent event — defined as kidney transplantation, long-term dialysis, use of SGLT2 inhibitors, or use of prohibited systemic glucocorticoids and other restricted or prohibited medications — were not included in the primary analysis.

The primary outcome was tested at a significance level of 0.01 (two-sided) at the interim analysis. Secondary outcomes will be tested in hierarchical fashion at the final analysis after all the patients in the main stratum have completed the double-blind portion of the trial (see the Supplementary Appendix). The exploratory outcome of the change in the urinary protein-to-creatinine ratio from baseline to week 36 in the SGLT2 inhibitor stratum was analyzed with the use of the same model as in the primary analysis. No hypothesis testing was performed.

Safety was assessed by collecting data on all adverse events, serious adverse events, and adverse events of special interest that occurred from the first dose up to 30 days after the last dose, unless otherwise specified. Statistical analyses were conducted with the use of SAS software, version 9.4.

RESULTS

TRIAL PATIENTS

The trial was conducted at 133 sites in 20 countries, and patients underwent randomization from March 2021 through April 2023. Overall, 653 patients were screened, of whom 404 met the inclusion criteria and were randomly assigned to receive atrasentan (0.75 mg per day) or placebo; 340 patients were recruited into the main stratum and 64 into the SGLT2 inhibitor stratum. Among the first 270 patients in the main stratum who completed 36 weeks of the trial, 135 underwent randomization in each trial group. A total of 10 patients (7.4%) in the atrasentan group and 22 (16.3%) in the placebo group discontinued the trial regimen; 4 patients (3.0%) and 11 (8.1%), respectively, discontinued the trial (Fig. 1).

The baseline characteristics of the patients were well balanced between the two groups (Table 1). The mean age of the patients was 44.9 years, and 41.1% were women. The mean duration of IgA nephropathy was 5.6 years, the mean eGFR was 58.9 ml per minute per 1.73 m^2, and the median 24-hour urinary protein-to-creatinine ratio was 1433. Most patients (98.5%) were using an ACE inhibitor or ARB (Table 1). The recruited patients were representative of the general population of patients with IgA nephropathy and were consistent with the patients involved in other trials (Table S1).

PRIMARY OUTCOME

In the atrasentan group, the geometric mean urinary protein-to-creatinine ratio changed from 1450.2 at baseline to 882.2 at week 36 (–38.1%; 95% confidence interval [CI], −43.9 to −31.7). In the placebo group, the geometric mean urinary protein-to-creatinine ratio changed from 1484.3 at baseline to 1374.8 at week 36 (–3.1%; 95% CI, –12.4 to 7.3). These findings corresponded to a

geometric mean between-group difference of −36.1 percentage points (95% CI, −44.6 to −26.4; P<0.001) (Fig. 2A). The reduction in the urinary protein-to-creatinine ratio in the atrasentan group was evident at week 6 and sustained through week 36 (Fig. 2B. The only intercurrent events that were observed and that led to censoring of data on the urinary protein-to-creatinine ratio in the primary analysis were initiation of restricted medication, which occurred in four patients (3.0%) in the atrasentan group and in seven patients (5.2%) in the placebo group. A prespecified sensitivity analysis including all values for urinary protein-to-creatinine ratio regardless of intercurrent events showed a geometric mean between-group difference (atrasentan vs. placebo) of −36.7 percentage points (95% CI, −44.8 to −27.3). The effect of atrasentan as compared with placebo was consistent across prespecified subgroups (Fig. S2).

EXPLORATORY EFFICACY OUTCOME

Among 29 patients in the SGLT2 inhibitor stratum who completed 36 weeks of the trial, the geometric mean percentage change in the urinary protein-to-creatinine ratio from baseline was −39.6% (95% CI, −54.1 to −20.4) in the atrasentan group (14 patients) and −3.4% (95% CI, −26.3 to 26.5) in the placebo group (15 patients). These findings corresponded to a geometric mean between-group difference of −37.4 percentage points (95% CI, −57.2 to −8.5) (Fig. S3).

SAFETY OUTCOMES

At week 36, the mean (±SD) change in blood pressure from baseline was −3.94±11.90 mm Hg (systolic) and −4.25±8.96 mm Hg (diastolic) in the atrasentan group and 2.67±12.25 mm Hg and 2.25±10.70 mm Hg, respectively, in the placebo group (Fig. 3A). At week 36, the mean change in body weight was −0.2±2.8 kg in the atrasentan group and −0.1±3.0 kg in the placebo group (Fig. 3B). At week 24, the mean change in the BNP level was 4.0±23.9 pg per millimeter in the atrasentan group and −0.6±18.8 pg per milliliter in the placebo group (Fig. 3C).

The percentage of patients with adverse events was similar in the atrasentan group (82.2%) and the placebo group (84.7%). Similarly, the percentage of patients with severe or serious adverse events and the percentage of patients who discontinued the trial regimen owing to an adverse event did not differ between the trial groups (Table 2). Of the most common adverse events, nasopharyngitis, peripheral edema, anemia, pyrexia, and upper respiratory tract infection were more common in the atrasentan group than in the placebo group. Some adverse events of special interest — anemia, fluid retention, and vasodilatation or hypotension — were more commonly reported with atrasentan than with placebo (Table 2). However, these events did not lead to discontinuation of the trial regimen, and no patient reporting anemia received a blood transfusion. There were no reports of cardiac failure, severe edema, or death during the trial. During the first 36 weeks of the treatment period, 10 patients (5.9%) in each trial group initiated diuretics.

DISCUSSION

In this prespecified interim analysis of an ongoing phase 3 clinical trial involving patients with IgA nephropathy, 36 weeks of treatment with atrasentan (0.75 mg per day) as compared with placebo reduced the urinary protein-to-creatinine ratio by 36.1 percentage points (P<0.001). This benefit is clinically meaningful, especially in the context of a high-risk trial population (patients had a total urinary protein excretion of ≥1 g per day at baseline, despite appropriate supportive care) and a reassuring safety and side-effect profile. Examination of the longer-term efficacy of atrasentan in reducing the decline in the eGFR as a key secondary outcome is ongoing and will be presented after all the patients in the main stratum have completed the double-blind treatment period of 136 weeks.

The effects of atrasentan were observed in a population of patients with IgA nephropathy who were treated according to current clinical-practice guidelines, including maximum tolerated doses of RAS inhibitors and lifestyle modification. These additive effects are consistent with the findings of an earlier report on sparsentan (a dual blocker of endothelin receptor and angiotensin receptor) in patients with IgA nephropathy.[12] Sparsentan did not significantly reduce the rate of eGFR decline over a period of 2 years. However, the change in

the eGFR from baseline to the end of the 4-week washout period was significantly reduced with sparsentan.[13]

During the conduct of the present trial, published post hoc analyses of two clinical trials showed the kidney-protective effects of SGLT2 inhibitors in patients with IgA nephropathy.[14,15] In our interim analysis, a separate exploratory stratum of patients who were receiving stable doses of RAS and SGLT2 inhibitors was therefore added. Exploratory interim analyses of that stratum showed similar effects of atrasentan in reducing proteinuria in the SGLT2 inhibitor stratum as compared with the main stratum. These initial data from the exploratory SGLT2 inhibitor stratum must be interpreted with caution, given the small numbers of patients. With a growing number of approved therapies, which now include an oral, targeted-release budesonide formulation (Nefecon) as well as sparsentan and iptacopan, there is an opportunity to deliver a multitargeted treatment regimen to simultaneously inhibit the key pathogenic pathways in IgA nephropathy, including endothelin system activation, to possibly slow or halt the progressive loss of kidney function of patients with IgA nephropathy.[13,16,17]

The current trial showed that atrasentan was associated with a favorable safety profile. Previous studies involving persons with chronic kidney disease and heart failure have shown that endothelin-receptor antagonists can precipitate or worsen preexisting heart failure, leading to premature termination of at least one trial involving patients with type 2 diabetes and chronic kidney disease with another endothelin-receptor antagonist.[18] Although there was a numerical imbalance in adverse events involving fluid retention in our trial, none of them led to discontinuation of the trial regimen. No cases of heart failure were reported, and instances of peripheral edema were generally balanced between the trial groups. In addition, changes in body weight and BNP levels over time did not differ substantially between the atrasentan and placebo groups. The above reported data reflect the low risk of clinically important fluid retention in this population of patients with IgA nephropathy. Adverse events involving anemia were more frequently reported with atrasentan than with placebo. This effect has been observed with other endothelin-receptor antagonists in which hemodilution has been thought to be a potential mechanism.[19] At the end of the trial, patients can continue atrasentan in an open-label extension study that will allow longer-term safety and efficacy monitoring.

The present prespecified interim analysis showed the efficacy of atrasentan using a surrogate outcome. Although the final results of the ALIGN trial will be needed to confirm that the proteinuria reduction seen with atrasentan translates to a reduction in eGFR decline, there is growing confidence in the urinary protein-to-creatinine ratio as a surrogate biomarker in IgA nephropathy.[20,21]

Our trial has certain limitations. Although we enrolled a representative cohort of patients with IgA nephropathy at high risk for kidney failure, the results cannot be generalized to patients with a total urinary protein excretion of less than 1 g per day. In addition, Black patients were underrepresented, which limits generalizability to these patients. Finally, the data presented here are limited to the primary outcome at the time of the 9-month interim analysis.

In this prespecified interim analysis of a multinational, randomized, controlled trial, atrasentan reduced proteinuria after 36 weeks of treatment without apparent safety issues in patients with IgA nephropathy at high risk for progression to kidney failure.

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