ALIGN Subgroup Analyses: Clinically Meaningful UPCR Reductions Seen across Subgroups

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KEY FINDINGS & CONCLUSIONS

- Atrasentan was superior to placebo in reducing proteinuria at Week 36, the primary endpoint (pre-specified interim analysis) of the ALIGN Phase 3 global clinical trial
  - Sensitivity analyses of the primary endpoint demonstrated the robustness of these results
  - Preliminary findings for an exploratory SGLT2i stratum were consistent with the main stratum
- Clinically meaningful proteinuria reductions were observed with atrasentan in all subgroups regardless of baseline demographic or disease characteristics
- Atrasentan was well tolerated with a favorable safety profile
- Results for the key secondary endpoint, eGFR change from baseline at Week 136 from the main stratum, will be presented after all patients have completed the double-blind study period
  - After Week 136, participants are offered the option to receive atrasentan in an open-label extension study

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INTRODUCTION

- IgA nephropathy (IgAN) is a heterogenous, progressive, rare kidney disease[1-3]
- Despite current standard of care, up to 50% of patients with IgAN develop kidney failure within 10–20 years of diagnosis. Even patients with proteinuria <1 g/day have a 30% risk of progressing to kidney failure within 10 years of diagnosis[3,4]
- Endothelin pathway dysregulation is associated with IgAN pathophysiology.[5]
- Endothelin A (ETA) receptor activation drives mesangial cell activation, kidney inflammation and fibrosis, and proteinuria, all hallmarks of IgAN.[5]
- Atrasentan is a potent and highly selective ETA receptor antagonist that demonstrated clinically meaningful reductions in proteinuria as well as a favorable safety and tolerability profile in patients with IgAN in the Phase 2 AFFINITY trial.[6]
- ALIGN (NCT04573478) is an ongoing Phase III, randomized, double-blind, placebo-controlled study comparing the efficacy and safety of atrasentan with placebo in patients with IgAN on optimized supportive care.[7,8]
- Presented are the Week 36 pre-specified interim analysis (primary endpoint) results of the ALIGN study.

METHODS

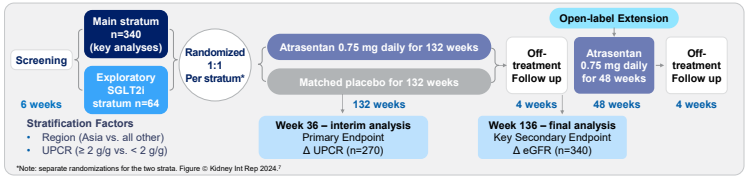
Study design

- Patients with biopsy-proven IgAN and proteinuria of ≥1 g/day were randomized to receive atrasentan 0.75 mg or placebo orally once daily for 132 weeks while on a stable dose of maximally tolerated/optimized RASi (**Figure 1**).

Key study endpoints

- **Primary endpoint:** change in proteinuria (UPCR based on 24-hour urine collection) from baseline to Week 36 in the main stratum.
  - *Subgroup analyses*: change in UPCR by demographic (gender, age, race, ethnicity and region) and baseline characteristics (baseline UPCR, BP, eGFR and diuretic use).
- **Key secondary endpoint:** change from baseline to Week 136 in eGFR in the main stratum.
- **Exploratory endpoint**: change in UPCR from baseline to Week 36 in the SGLT2i stratum
- **Safety endpoints:** type, incidence, severity, seriousness, and relatedness of TEAE and TEAESI

Figure 1. Study design



*Note: separate randomizations for the two strata. Figure © Kidney Int Rep 2024.[7]

Key Inclusion criteria

- Male/female ≥18 years
- Biopsy-proven IgAN
- On optimized/maximally tolerated RASi
- Total urine protein ≥1 g/day
- eGFR ≥30 mL/min/1.73m²

Key Exclusion criteria

- CKD from another cause
- BNP >200 pg/mL or Hgb <9g/dL
- History of organ transplantation
- Non-RASi IgAN treatment
- RPGN or IgA vasculitis
- Nephrotic syndrome

RESULTS

- In total 653 patients were screened, of whom 404 met the eligibility criteria (340 patients were recruited into the main stratum and 64 into the exploratory SGLT2i stratum) and were randomized. Results from the first 270 patients who were randomized in the main stratum and completed 36 weeks of the trial are reported here.
- Demographics and patient characteristics were well balanced at baseline (**Table 1**).

Table 1. Demographic and clinical characteristics of the first 270 patients in the main stratum

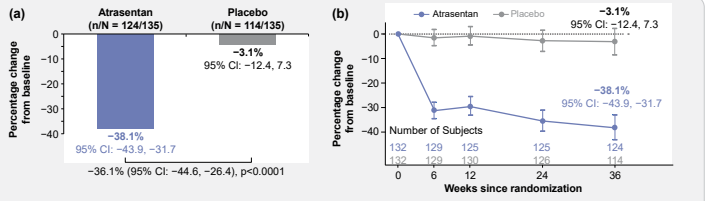
Parameters	Atrasentan 0.75 mg QD (N=135)	Placebo (N=135)	Total (N=270)
Age, mean (SD)	45.7 (12.9)	44.1 (11.0)	44.9 (12.0)
Female, n (%)	54 (40.0)	57 (42.2)	111 (41.1)
Region, n (%)			
Asia	64 (47.4)	63 (46.7)	127 (47.0)
Non-Asia	71 (52.6)	72 (53.3)	143 (53.0)
Duration of disease, years, mean (SD)	5.1 (5.4)	6.1 (6.0)	5.6 (5.7)
Systolic BP, mmHg, mean (SD)	125.4 (13.3)	122.9 (12.3)	124.2 (12.9)
Diastolic BP, mmHg, mean (SD)	79.6 (9.9)	78.7 (9.0)	79.1 (9.4)
24-hr total UPE, mg/day, median (Q1, Q3)	1847 (1314, 2776)	1851 (1329, 2550)	1848 (1328, 2664)
24-hr UPCR, mg/g, median (Q1, Q3)	1436 (1007, 1989)	1429 (1101, 1918)	1432 (1063, 1956)
eGFR, mL/min/1.73m², mean (SD)	58.3 (23.8)	59.5 (24.4)	58.9 (24.0)
RASi usage at baseline, n (%)			
ACEi use only	37 (27.4)	37 (27.4)	74 (27.4)
ARB use only	97 (71.9)	95 (70.4)	192 (71.1)

Table © NEJM 2024.[8]

Efficacy

- Atrasentan showed a statistically significant and clinically meaningful proteinuria reduction of 36.1% (95% CI: 26.4%, 44.6%; p<0.0001) relative to placebo, after 36 weeks of treatment (**Figure 2**)
  - **Sensitivity analysis** of the primary endpoint including all 24 hr UPCR values regardless of restricted medication use, chronic dialysis or kidney transplant was consistent with the primary analysis; relative mean percentage change in UPCR from baseline for atrasentan compared with placebo: −36.7 (95% CI: −44.8, −27.3).
  - Proteinuria reduction was of similar magnitude regardless of age, sex, race, ethnicity or region, and baseline levels of proteinuria, eGFR, BP or diuretic usage (**Figure 3**)
- **Exploratory SGLT2i stratum**: relative mean percentage change in UPCR from baseline after 36 weeks of treatment between atrasentan and placebo was −37.4 (95% CI:−57.2, −8.5).

Figure 2. Change in 24-Hour UPCR at a) Week 36 and b) over time in the main stratum

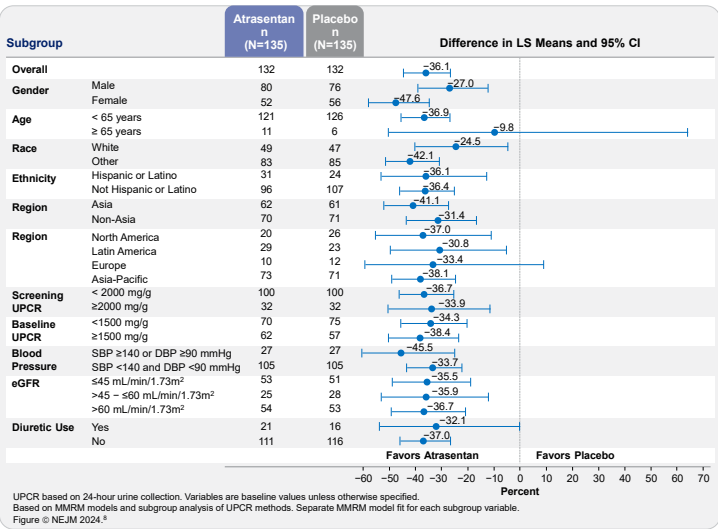


Based on a Mixed Model Repeated Measures analysis with the change from baseline of natural log UPCR at each post-baseline timepoint as outcomes; UPCR values are censored (excluded) for subjects with intercurrent events (i.e., restricted medication use, chronic dialysis, kidney transplant) beginning at the start date of the earliest event. Missing UPCR values implicitly imputed assuming Missing at Random. The N's in the figure reflect the number of subjects whose data at that timepoint are included in the MMRM analysis; Subjects with no post-baseline data are excluded at baseline. Figure © NEJM 2024.[8]

Safety

- Overall, atrasentan was well tolerated with a favorable safety profile (**Table 2**).
- Most TEAESIs were mild in severity; there were no serious TEAESIs. There were no TEAESIs that lead to study drug discontinuation (**Table 2**).

Figure 3. 24-Hour UPCR Week 36 percentage change from baseline in LS means by subgroups: MMRM analysis primary efficacy set



UPCR based on 24-hour urine collection. Variables are baseline values unless otherwise specified.
Based on MMRM models and subgroup analysis of UPCR methods. Separate MMRM model fit for each subgroup variable.
Figure © NEJM 2024.[8]

Table 2. Adverse events and adverse events of special interest in the main stratum

Events	Atrasentan 0.75 mg QD N=169	Placebo N=170
Subjects with any TEAE, n (%)	**139 (82.2)**	**144 (84.7)**
COVID-19	35 (20.7)	37 (21.8)
Nasopharyngitis	17 (10.1)	10 (5.9)
Oedema peripheral	15 (8.9)	11 (6.5)
Anaemia	11 (6.5)	2 (1.2)
Pyrexia	11 (6.5)	7 (4.1)
Upper respiratory tract infection	11 (6.5)	9 (5.3)
Subjects with serious TEAE, n (%)	10 (5.9)	11 (6.5)
Subjects with severe TEAE, n (%)	12 (7.1)	10 (5.9)
Subjects with any TEAE leading to study drug discontinuation, n (%)	6 (3.6)	6 (3.5)
TEAESI category*, n (%)		
Anaemia**	14 (8.3)	4 (2.4)
Cardiac Failure	0	0
Fluid Retention	19 (11.2)	14 (8.2)
Vasodilation/Hypotension	10 (5.9)	7 (4.1)
Subjects With Any TEAESI, n (%)	38 (22.5)	24 (14.1)
Any Serious TEAESI, n (%)	0	0
Any Moderate or Severe TEAESI, n (%)	10 (5.9)	11 (6.5)
Any TEAESI leading to drug discontinuation	0	0

*AESIs were identified using FDA Medical Query category **No patient with anaemia required blood transfusion;
Table © NEJM 2024.[8]

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Abbreviations
ACEi, angiotensin-converting enzyme inhibitor; AESI: adverse event of special interest; ARB, angiotensin receptor blocker; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; IgAN, IgA nephropathy; LS, least squares; QD, once daily; MMRM, Mixed Model Repeated Measures; RASi, renin-angiotensin system inhibitor; SD, standard deviation, SGLT2i, sodium glucose transporter-2; TEAE, treatment emergent adverse events; TEAESI, treatment emergent adverse event of special interest; UPCR, urine protein-creatine ratio: UPE, urine protein excretion

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