A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Atrasentan in Patients with IgA Nephropathy (The ALIGN Study)

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Abstract

Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis globally and an important cause of chronic kidney disease (CKD). Up to 40% of IgAN patients are at risk of progressing to end-stage kidney disease (ESKD) and proteinuria is the strongest predictor of progression. There are no approved therapies for IgAN, leaving an important need for new strategies to lower proteinuria and preserve kidney function in high-risk patients.
Endothelin A (ETA) receptor activation drives proteinuria, along with kidney inflammation and fibrosis. Atrasentan, a potent and selective ETA antagonist, has been studied extensively in >5,000 patients with type 2 diabetes and kidney disease (DKD), demonstrating clinically significant and sustained reductions in proteinuria when administered on top of a maximum tolerated dose of RAS inhibitor (RASi). In a global Phase 3 outcome study in DKD (SONAR), atrasentan demonstrated a 35% reduced risk of the primary composite outcome of doubling of serum creatinine or end stage kidney disease (95% CI: 0.49, 0.88; P = 0.005). The most common adverse event was fluid retention.
Selective ETA blockade represents a promising approach to reduce proteinuria and preserve kidney function in high risk IgAN patients.

Objective: A global, phase 3, double-blind, placebo-controlled study is currently enrolling to determine the effect of atrasentan in IgAN patients at high risk of kidney function loss.

Methods: Approximately 320 patients across North America, South America, Europe, and Asia-Pacific with biopsy-proven IgAN will be randomized to receive 0.75 mg atrasentan or placebo daily for 132 weeks. Patients will continue receiving a maximally tolerated and stable dose of a RAS inhibitor as standard of care. The study will also include patients that are unable to tolerate RAS inhibitor therapy. Additional eligibility criteria include urine protein creatinine ratio (UPCR) ≥1 g/g and eGFR ≥30 mL/min/1.73 m^2. Participants will have study assessments over two and a half years with options for remote study visits using telemedicine and home health visits. The primary objective is to evaluate the effect of atrasentan versus placebo on proteinuria at Week 24. Secondary objectives include evaluating the change from baseline in eGFR, safety, and tolerability, and quality of life.

Study Background

Atrasentan

- Atrasentan is a potent endothelin A (ET_A) receptor antagonist (Ki = 0.034 nM) with >1,800 fold selectivity over ET_B (Ki = 63.3 nM).[1]
- Blocking ET_A leads to rapid and sustained reductions in proteinuria and has direct anti-inflammatory and anti-fibrotic effects.[2]
- Atrasentan has been studied extensively in more than 5,300 patients with type 2 diabetes and chronic kidney disease (DKD), demonstrating clinically significant and sustained reductions in proteinuria when administered on top of a maximum tolerated dose of a RAS inhibitor (RASi).[3, 4]
- In a Phase 2 study in DKD (RADAR), atrasentan reduced urine albumin-creatinine ratios by an average of 35% (95% confidence interval [CI]: 24, 45; P = 0.001).[3]
- In a global Phase 3 outcome study in DKD (SONAR), the atrasentan treatment group demonstrated a 35% reduced risk of the primary composite outcome of doubling serum creatinine or end stage kidney disease (95% CI: 0.49, 0.88; P = 0.005).[4]

Figure 1. UACR change in the percent geometric mean from baseline to recovery in RADAR

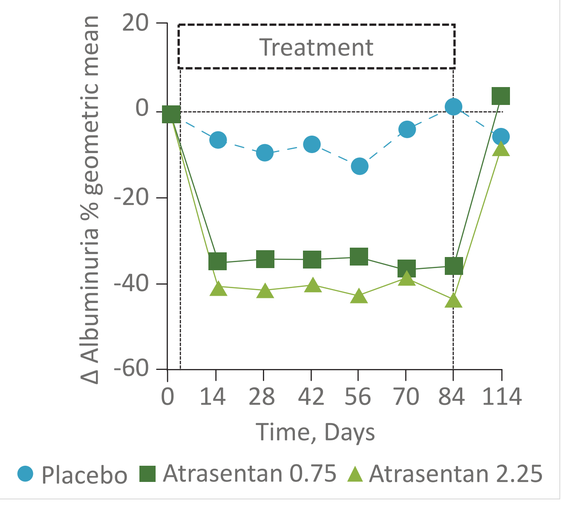
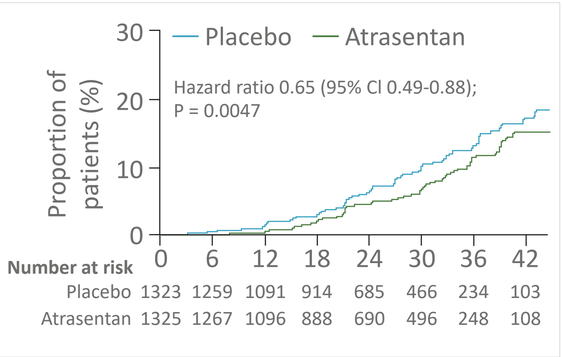


Figure 2. Effects of atrasentan on the primary composite renal outcome in SONAR



IgA Nephropathy

- IgA nephropathy (IgAN) is the most common primary glomerulonephritis globally and an important cause of chronic kidney disease (CKD). Up to 45% of IgAN patients are at risk of progressing to end-stage kidney disease (ESKD) and proteinuria is the strongest predictor of progression.[5,6]
- There are no approved therapies for IgAN and no clear consensus on second line therapy to manage residual proteinuria despite maximally tolerated RAS inhibition. [KDIGO, 2012]
- Immunosuppression, with steroids or other agents has been studied extensively; however, the efficacy of immunosuppression is inconsistent and is associated with significant safety and tolerability concerns, leaving an important need for new strategies to lower proteinuria and preserve kidney function in high risk patients[7,8]

Rationale for Atrasentan Use in IgA Nephropathy

- ET_A activation results in mesangial cell proliferation and extracellular matrix and cytokine production[9], podocyte injury[10], proteinuria[4] and tubulointerstitial inflammation and fibrosis[12], all hallmark characteristics of progressive IgAN.
- The benefit of selective ET_A blockade in IgAN has been clinically validated in an exploratory trial of sitaxsentan demonstrating significant reduction in proteinuria and intraglomerular pressure in CKD patients on standard of care therapy[13]

Proteinuria as a Surrogate Endpoint for Accelerated Approval

- Proteinuria is the single most important predictor of the rate of renal progression in IgAN[6]
- Trial-level analyses of data from 13 randomized-controlled trials show a strong association between treatment effects on proteinuria with hard renal outcomes in IgAN[14]
- Proteinuria reduction is recognized as a reasonably likely surrogate endpoint by the FDA to support accelerated regulatory approval[14]

Study Methods

Study Objectives

The Phase 3 ALIGN trial will assess the efficacy, safety and tolerability of atrasentan in IgAN patients at risk of progressive kidney function loss, despite optimized RAS blockade.

Study Endpoints

- The primary endpoint for the ALIGN study is change in proteinuria (UPCR from a 24-hr urine collection) from baseline to week 24.
- The key secondary endpoint for the study is change in eGFR from baseline to week 136 (4 weeks following discontinuation of treatment).
- Additional secondary outcome measures include:
  - Rate of change in eGFR during 2 years on treatment at Week 12 through to Week 120 and from baseline to Week 136.
  - Percent of subjects achieving proteinuria < 1 g/day at Week 24 and 40% reduction in UPCR from baseline.
  - Percent of subjects experiencing at least a 30% reduction in eGFR or reach ESKD during the study.
  - Percent of subjects experiencing at least a 40% reduction in eGFR or reach ESKD during the study.

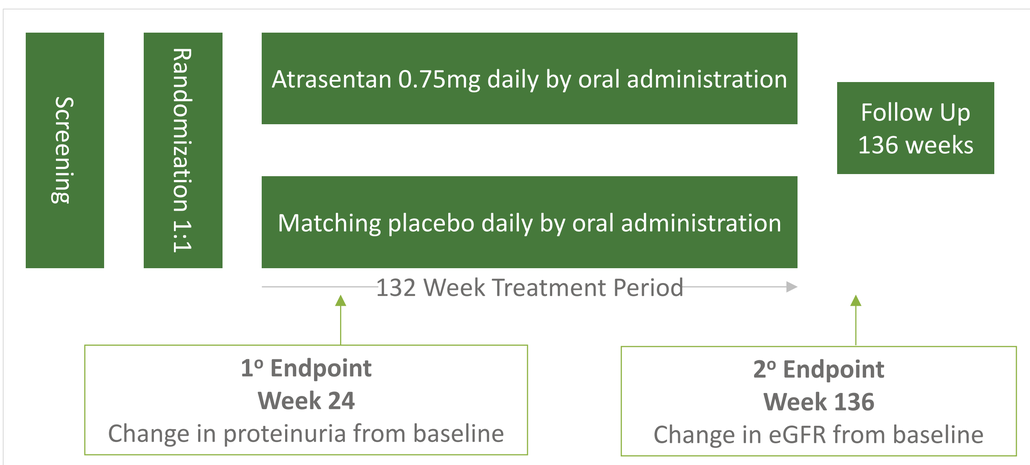
Study Design

- Approximately 320 patients across North America, South America, Europe, and Asia-Pacific with biopsy-proven IgAN will be randomized to receive 0.75 mg atrasentan or placebo daily for 132 weeks.
- Patients will receive a maximally tolerated and stable dose of a RASi.
  - The study will include patients who are unable to tolerate RASi.
- Subjects will have assessments of safety and efficacy over 2½ years
  - Where allowed by local regulations, options for remote study visits using telemedicine and home health may be offered.
  - Provides a flexible solution for patients and clinicians in the era of COVID-19 and reduces the burden to patients for trial participation.
- Subjects who complete the study may be eligible to enroll in an open-label treatment trial with atrasentan.

Study Eligibility & Schema

Key Eligibility Criteria

- Age 18 and older
- Biopsy proven IgAN - no time limit on biopsy
- Stable, optimized dose of ACE inhibitor or ARB for ≥ 12 weeks or unable to tolerate RASi
- UPCR ≥1 g/g based on first morning void
- eGFR of at least 30 mL/min/1.73m^2
- No use of systemic immunosuppressants, such as steroids, for more than 2 weeks in the past 3 months
- No current diagnosis with another chronic kidney disease, including diabetic kidney disease
- No history of kidney or other transplantation
- No history of heart failure or a previous hospital admission for fluid overload



- Virtual trial options may include telemedicine and home health nurse visits
- Patient compensation for 24-hour urine collection and reimbursement for trial-related expenses
- Open label extension study available to participants completing the study
- Currently selecting trial sites in North America, South America, Europe, and Asia-Pacific. Currently enrolling

ClinicalTrials.gov Identifier: NCT04573478

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First Author Disclosures

Category	Disclosure Information
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