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

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Abstract

Introduction:
IgA nephropathy (IgAN) is the most common primary glomerulonephritis. Up to 40% of patients with IgAN are at risk of progressing to end-stage kidney disease (ESKD); proteinuria is the strongest predictor of progression. Endothelin A receptor (ETA) activation promotes proteinuria, along with kidney inflammation and fibrosis. Atrasentan, a potent and selective ETA antagonist, has been studied in >5,000 patients in a global phase 3 outcome clinical trial in patients with diabetic kidney disease who were on a maximum tolerated dose of RAS inhibitor (RASi). Results showed a 35% reduced risk of the primary composite outcome of doubling of serum creatinine or ESKD (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 patients with IgAN at high risk of progression.

Objective:
A global, phase 3, double-blind, placebo-controlled study is in progress to determine the effect of atrasentan on reduction of proteinuria and slowing down kidney function loss in patients with IgAN at high risk of kidney disease progression.

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 RASi as standard of care. The study will also include a group of patients that are unable to tolerate RASi therapy. Additional eligibility criteria include 24 hour urine protein ≥1 g/day 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 change in proteinuria at Week 24. Secondary objectives include change from baseline in eGFR, safety, and tolerability, and quality of life.

Results:
The trial is in progress and results will be presented when available.

Conclusions:
Potent and selective endothelin A antagonism by atrasentan is a promising approach for treatment of IgAN.
This abstract has been presented at WCN 2021, ERA-EDTA 2021, IIGANN 2021 and ASN 2021.

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 ETA 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 from baseline (Geometric Mean)

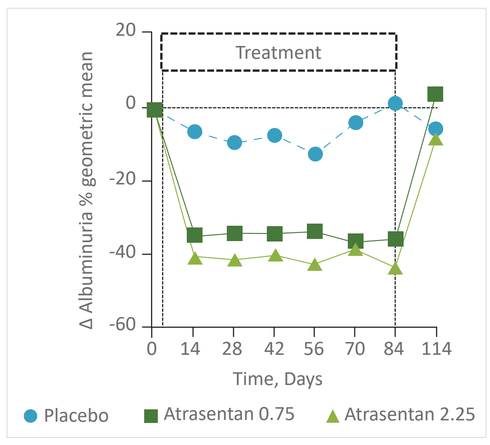
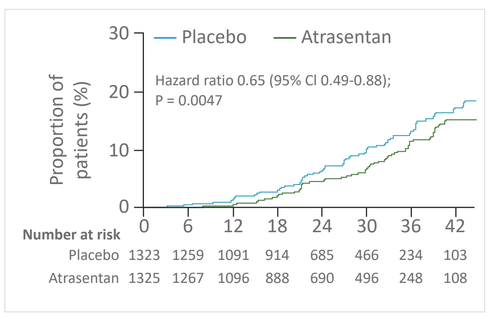


Figure 2. Effects of atrasentan on the primary composite renal outcome in SONAR

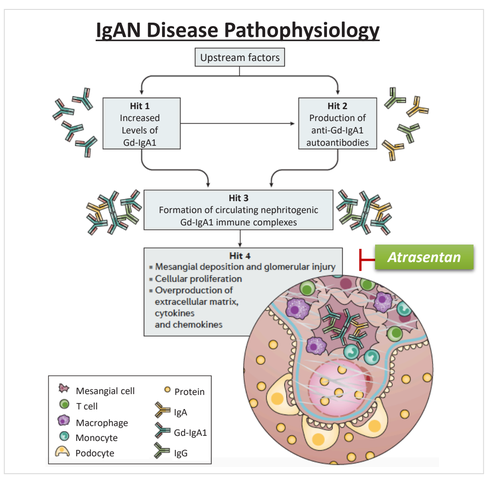


IgAN

- 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.[5,6]
- 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 IgAN

- ET_A activation results in mesangial cell proliferation, extracellular matrix, cytokine production[9], podocyte injury[10], proteinuria[4], tubulointerstitial inflammation & 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 evaluate the efficacy, safety and tolerability of atrasentan in patients with IgAN at high 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.

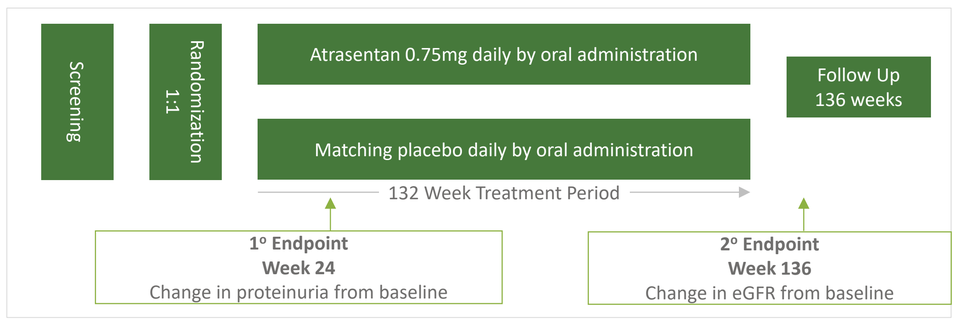
Study Design

- 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 a subset of patients (up to 5%) 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
- Total urine protein ≥1 g/day based on 24-hour urine collection
- eGFR of at least 30 mL/min/1.73m^2
- No use of systemic immunosuppressants, including 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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