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, with up to 40% of patients with IgAN are at risk of progressing to end-stage kidney disease (ESKD). Studies have shown that the risk of ESKD is increased by 150% with proteinuria >300 mg/day.1

Objective: To evaluate the efficacy and tolerability of atrasentan in patients with IgAN who are at high risk of progressive kidney function loss.

Methods: Approximately 320 patients across North America, South America, Europe, and Asia-Pacific with biopsy-proven IgAN are being randomized to receive 0.75 mg atrasentan or placebo daily for 132 weeks. Patients will continue receiving a maximally 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. Selecta ETA blockade represents a promising approach to reduce proteinuria and preserve kidney function in high risk patients.

IgNephropathy

• In a global Phase 3 outcome study in 1,800 patients across North America, South America, Europe, and Asia-Pacific with biopsy-proven IgAN who were on a maximum tolerated dose of a RASi as standard of care. The study will also include a subset of patients who are unable to tolerate RASi.
• Additional secondary outcome measures include:
  – Rate of change in eGFR during 2 years on treatment at Week 12 through to Week 120 and from Week 120 to Week 24.
  – Percent of subjects experiencing a ≥30% reduction in eGFR at end of RASi treatment.
  – Percent of subjects experiencing at least a 30% reduction in eGFR at end of RASi treatment.

Study Design

• Approximately 400 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.
• A placebo-controlled, double-blind, randomized, double-dummy, parallel-group, multicenter trial (SONAR) of atrasentan treatment in patients with type 2 diabetes and chronic kidney disease (SONAR), demonstrating clinically relevant and sustained reductions in proteinuria and atrasentan is well tolerated.

Study Background

Atrasentan (2.25 mg atrasentan) is a potent and selective ETA antagonist, has been shown to reduce proteinuria and preserve kidney function in high risk patients.

Key Eligibility Criteria

• Age ≥18 years and older
• Proteinuria >300 mg/day at screening
• Baseline plasma creatinine ≤150% of the upper limit of normal
• Serum creatinine level must be ≤1.5 mg/dL (133 μmol/L)

Proteinuria as a Surrogate Endpoint for Accelerated Approval

• Proteinuria ≥1 g/day was associated with increased risk of ESRD leading to transplantation and death in patients with IgAN (Sonar trial).
• Proteinuria reduction was a primary endpoint in SONAR (2019). Proteinuria reduction ≥30% was associated with improved kidney outcomes.

Study Objectives

The Phase 2b trial will evaluate the efficacy, safety and tolerability of atrasentan in patients with IgA nephropathy with baseline proteinuria ≥1 g/day, double-blind, multi-center RCT.

Study Endpoints

• The primary endpoint for the 2b study is change in proteinuria (percent change from baseline) at Week 24, for a 24-week duration. Patients will continue to receive the same treatment up to 132 weeks.
• The secondary key endpoint for the study is change in eGFR from baseline to week 20 (6 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 Week 120 to Week 24.
  – Percent of subjects experiencing a ≥30% reduction in eGFR at end of RASi treatment.
  – Percent of subjects experiencing at least a 30% reduction in eGFR at end of RASi treatment.

Baseline characteristics will be compared between the atrasentan and placebo arms using Student’s t-test for continuous variables and Fisher’s exact test for categorical variables.

Nephropathy (The ALIGN Study)

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References


First Author Disclosures

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