A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Atrasentan in Patients with IgA Nephropathy (The ALIGN Study)
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Study Background
Atrasentan is a potent endothelin A (ET1) receptor antagonist (Ki = 0.005 nM) with >1,800 fold selectivity over ETB (Ki = 63.3 nM).1

Blocking ET1 results in reduced urinary albumin excretion by an average of 35% (95% confidence interval [CI]: 24, 40; P < 0.001).1

Atrasentan has been studied extensively in >5,000 patients with type 2 diabetes and chronic kidney disease (DKD), demonstrating clinically significant and sustained reductions in proteinuria when administered on top of a maximally tolerated dose of a RAS inhibitor (RASi).2

In a global Phase 3 outcome study in SONAR, the atrasentan treatment group showed a 40% reduction of the primary composite outcome of doubling of serum creatinine or end stage kidney disease (95% CI: 9, 24; 0.005).4

The benefit of selective ETA blockade in IgAN has been clinically validated in an exploratory trial of sitaxsentan demonstrating no evidence of improvement in proteinuria or other renal outcomes in IgAN (95% confidence interval [CI]: 24, 45; P = 0.19).14

IgA Nephropathy
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.4

The benefit of selective ETA blockade in IgAN has been clinically validated in an exploratory trial of sitaxsentan demonstrating no evidence of improvement in proteinuria or other renal outcomes in IgAN (95% confidence interval [CI]: 24, 45; P = 0.19).14

Study Objectives
The primary objective for the ALIGN study is change in proteinuria (UPCR from a 24-h urine collection) from baseline to week 24.

Secondary objectives include evaluating the change from baseline in:
- Rate of change in eGFR during 2 years on treatment at Week 12 through to Week 120 and from baseline to Week 136
- Rate 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
An exploratory trial of 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 152 weeks.

Patients will receive a maximally tolerated and stable dose of a RASi as standard of care. The study will also include patients who are unable to tolerate RASi therapy. Additional eligibility criteria include urine protein creatinine ratio (UPCR) ≥1 mg/g and eGFR ≥30 mL/min/1.73 m2. Participants will have study assessments every 4 weeks and will have options for remote study visits using telemedicine and home health visits. The primary outcome is the rate of change in proteinuria versus placebo on UPCR at Week 24. Secondary objectives include examining the change from baseline in eGFR, safety, and tolerability, and quality of life.

Study Endpoints
The primary endpoint for the ALIGN study is change in proteinuria (UPCR from a 24-h urine collection) from baseline to week 24.

• The key secondary endpoint for the study is change in eGFR from baseline to week 136 (if no worsening 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
- Rate 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 Eligibility & Schema
Key Eligibility Criteria
- Age 18 and older
- Biopsy-proven IgA - no time limit on biopsy
- Stable, optimized dose of ACE inhibitor or ARB for ≥12 weeks or unstable RASi (HFrEF: <100 mg based on first morning void)
- eGFR of ≥30 mL/min/1.73 m2
- No use of systemic immunosuppressants, such as steroids, for more than 2 weeks in the past 3 months
- Aldosterone antagonist not used in last 6 months
- No previous 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

Study Outcomes
- Primary endpoint: Change in proteinuria from baseline
- Secondary endpoints: Change in eGFR during 2 years on treatment
- Safety and tolerability
- Quality of life

At 12-152 Week Treatment Period

Follow Up 130 weeks

Reporting placebo daily by oral administration

- Virtual trial options may include telemonitoring and telemedicine
- Patient can choose 24-hour urine collection, no clinic visit, or home health visits for trial-related expenses

Open label extension study: available to participants completing the study

ClinicalTrials.gov identifier: NCT04517678

References

The HDL-4 and HDL-5 are tools by Chinook Therapeutics, Inc.