Atrasentan in Patients with Proteinuric Glomerular Diseases (The AFFINITY Study)

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CHINOOK THERAPEUTICS

Abstract

Background: Glomerular diseases are a leading cause of morbidity and mortality worldwide. Immunoglobulin A nephropathy (IgAN), focal segmental glomerulosclerosis (FSGS), Alport syndrome, and diabetic kidney disease (DKD) are all characterized by proteinuria, a strong predictor of disease progression and end-stage kidney disease (ESKD). Currently, there are limited therapies and despite the recent approval of sodium glucose co-transporter 2 inhibitors (SGLT2i), residual risk remains. It is known that Endothelin A (ETA) receptor activation drives proteinuria, inflammation and fibrosis through a common pathogenic pathway. Atrasentan, a potent and selective ETA antagonist, has demonstrated clinically significant proteinuria reduction in over 5,300 patients with DKD when administered on top of a maximum tolerated dose of RAS inhibitor (RASi). It was overall well tolerated, and the most common adverse event was fluid retention.

Selective ETA blockade represents a potential approach to reduce proteinuria and preserve kidney function in proteinuric glomerular diseases.

Objective: A global, phase 2, open-label basket study is in progress to evaluate the efficacy and safety of atrasentan in patients with IgAN, FSGS, Alport syndrome and DKD who are at risk of progressive loss of kidney function.

Methods: Approximately 80 patients in the United States, Australia, South Korea, Spain, Italy, and the United Kingdom with proteinuric glomerular diseases are being enrolled in a basket study to receive 0.75 mg atrasentan orally for 52 weeks. Four cohorts are planned, each consisting of approximately 20 patients with the following diseases: IgAN, Alport syndrome, FSGS, and DKD. Patients must be receiving a maximally tolerated and stable dose of RASi and patients with DKD must also be on a stable dose of a SGLT2i. Proteinuria must be present in all patients: IgAN (urine protein creatinine ratio [UPCR] between 0.5 and < 1.0 g/g), FSGS (UPCR > 1.5 g/g), Alport syndrome (UPCR > 0.5 g/g), and DKD (urine albumin creatinine ratio [UACR] ≥ 0.5 g/g). Patients must also have an eGFR ≥ 30 mL/min/1.73 m^2 (≥ 45 mL/min/1.73 m^2 for patients in the DKD cohort). Patients will have study assessments over 1 year with options for remote study visits using telemedicine and home health visits. The primary objective is to evaluate change in proteinuria (IgAN, FSGS, AS) or albuminuria (DKD) from Baseline to Week 12. Key exploratory objectives include changes in eGFR from Baseline to Week 52 and changes in audiology assessments in patients with Alport syndrome.

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)

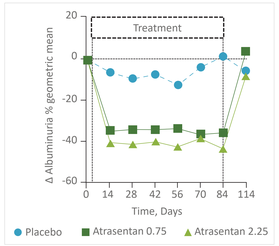
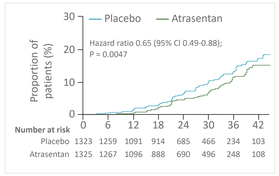
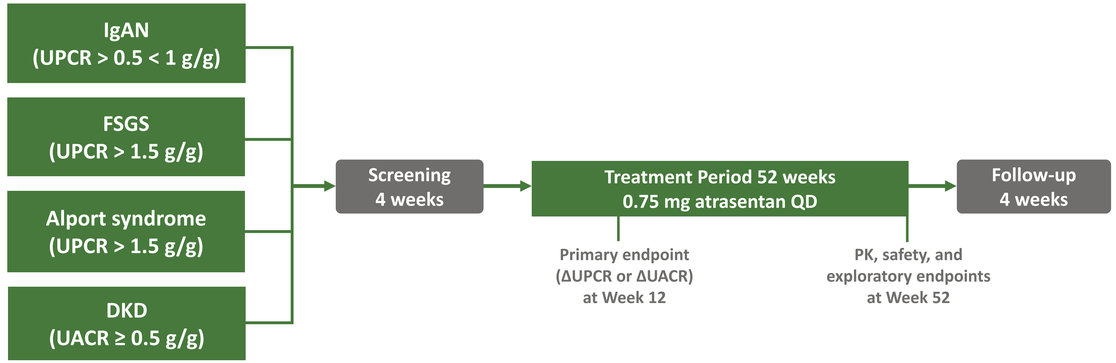


Figure 2. Effects of atrasentan on the primary composite renal outcome in SONAR



Study Design

A Phase 2, Basket Study of Atrasentan in Patients with Proteinuric Kidney Disease



- Open-label design with approximately 20 patients per cohort.
- Complimentary study at select ALIGN sites (see ALIGN Study Poster)
  - 40 sites in 6 countries (US, Australia, South Korea, UK, Spain, and Italy)
- Primary endpoint: change from baseline in UPCR (Cohorts 1-3) or in UACR (Cohort 4).
- Multiple populations and indications in a single study to demonstrate potential for proteinuria reduction in different CKD populations of varying underlying etiologies.

References

1. Wu-Wong, J.R., et al., Pharmacology of endothelin receptor antagonists ABT-627, ABT-546, A-182086 and A-192621: in vitro studies. *Clin Sci (Lond)*, 2002. 103 Suppl 48: p. 107s-111s.
2. Kohan, D.E. and M. Barton, Endothelin and endothelin antagonists in chronic kidney disease. *Kidney Int*, 2014. 86(5):p.896-904.
3. de Zeeuw, D., et al., The endothelin antagonist atrasentan lowers residual albuminuria in patients with type 2 diabetic nephropathy. *J Am Soc Nephrol*, 2014. 25(5): p. 1083-93.
4. Heerspink, H.J.L., et al., Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease(SONAR): a double-blind, randomised, placebo-controlled trial. *The Lancet*, 2019. 393(10184): p. 1937-1947.