

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



CHINOOK
THERAPEUTICS

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Abstract

Introduction:

Glomerular diseases are a leading cause of morbidity and mortality worldwide and are characterized by proteinuria, a strong predictor of disease progression and end-stage kidney disease. 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 glomerular injury, inflammation, and fibrosis through a common pathogenic pathway. Atrasentan, a potent and selective ETA receptor antagonist that has shown clinically significant reduction in proteinuria and risk of kidney failure in a study of over 5,300 patients with diabetic kidney disease (DKD), represents a promising therapy to reduce proteinuria and preserve kidney function in proteinuric glomerular diseases.

Objective:

Global, phase 2, open-label basket study to study the efficacy and safety of atrasentan in patients with proteinuric glomerular diseases.

Methods:

Patients in the United States, Australia, South Korea, Spain, Italy, and the United Kingdom with proteinuric glomerular diseases will be enrolled in an open labelled basket study to receive 0.75 mg atrasentan orally for 52 weeks. Four cohorts are planned with 20 patients in each cohort: IgA Nephropathy (IgAN), Alport syndrome (AS), Focal Segmental Glomerular Disease (FSGS), and DKD. Patients must be receiving a maximally tolerated and stable dose of Renin Angiotensin System inhibitor (RASi) and patients with DKD must also be on a stable dose of a SGLT2i. Proteinuria inclusion criteria: 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). Participants will have study assessments over one year with options for remote study visits using telemedicine and home health visits. The primary objective is to evaluate the 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.

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 proteinuric glomerular diseases. This abstract has been presented previously at WCN 2021, ERA-EDTA 2021, IIGANN 2021 and ASN 2021.

Study Background

Atrasentan

- Atrasentan is a potent endothelin A (ET_A) receptor antagonist (K_i = 0.034 nM) with >1,800-fold selectivity over ET_B (K_i = 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 from baseline (Geometric Mean)

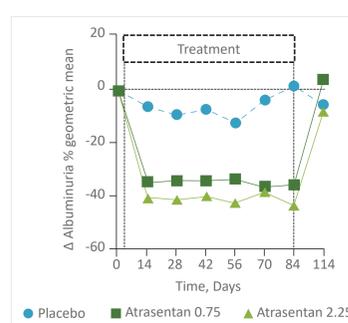
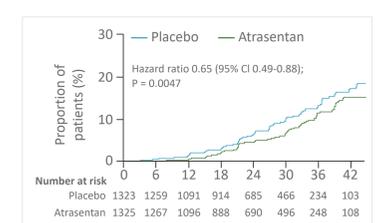
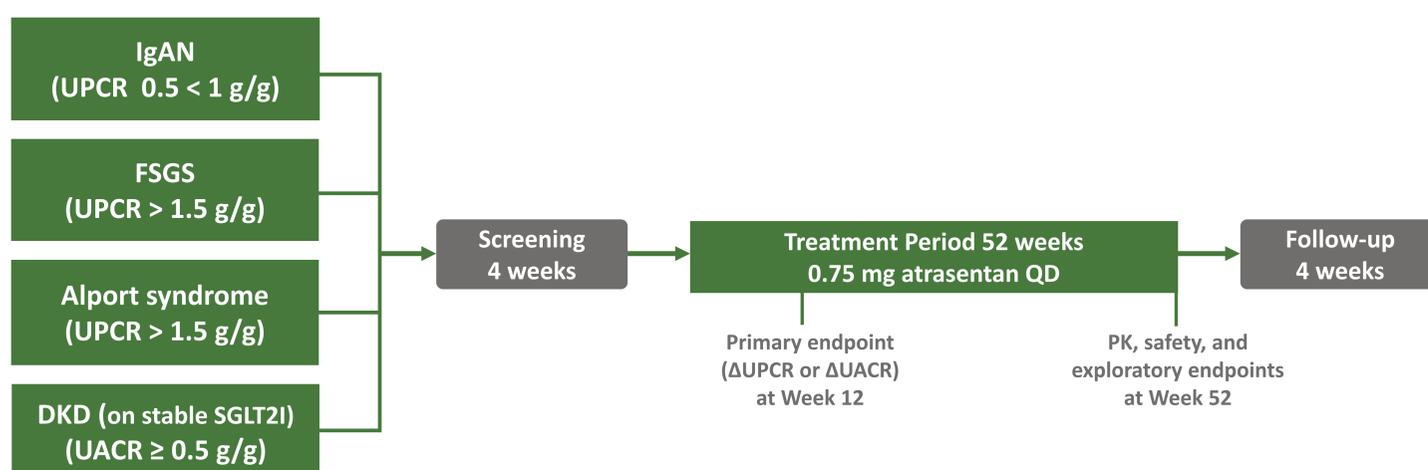


Figure 2. Effects of atrasentan on the primary composite renal outcome in SONAR



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

- 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.
- Kohan, D.E. and M. Barton, Endothelin and endothelin antagonists in chronic kidney disease. *Kidney Int*, 2014. 86(5):p.896-904.
- 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.
- 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.