

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



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Background

Glomerular diseases are the leading cause of end stage kidney disease (ESKD) worldwide. Immunoglobulin A nephropathy (IgAN), focal segmental glomerulosclerosis (FSGS), Alport syndrome, and diabetic kidney disease (DKD) are all characterized by proteinuria, which is a strong predictor of disease progression and ESKD. Currently, there are no approved therapies for IgAN, FSGS, or Alport syndrome and despite the recent approval of sodium glucose co-transporter 2 inhibitors (SGLT2i), residual risk in DKD remains high, leaving an important unmet need for new therapies to lower proteinuria and preserve kidney function in high-risk patients. Endothelin A (ETA) receptor activation drives proteinuria, along with kidney inflammation and fibrosis. Atrasentan, a potent and selective ETA antagonist, targets a key pathogenic pathway common to the progression of proteinuric glomerular disease of different underlying etiologies. Atrasentan has been studied in >5,000 patients with DKD, showing clinically significant and sustained reductions in proteinuria 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

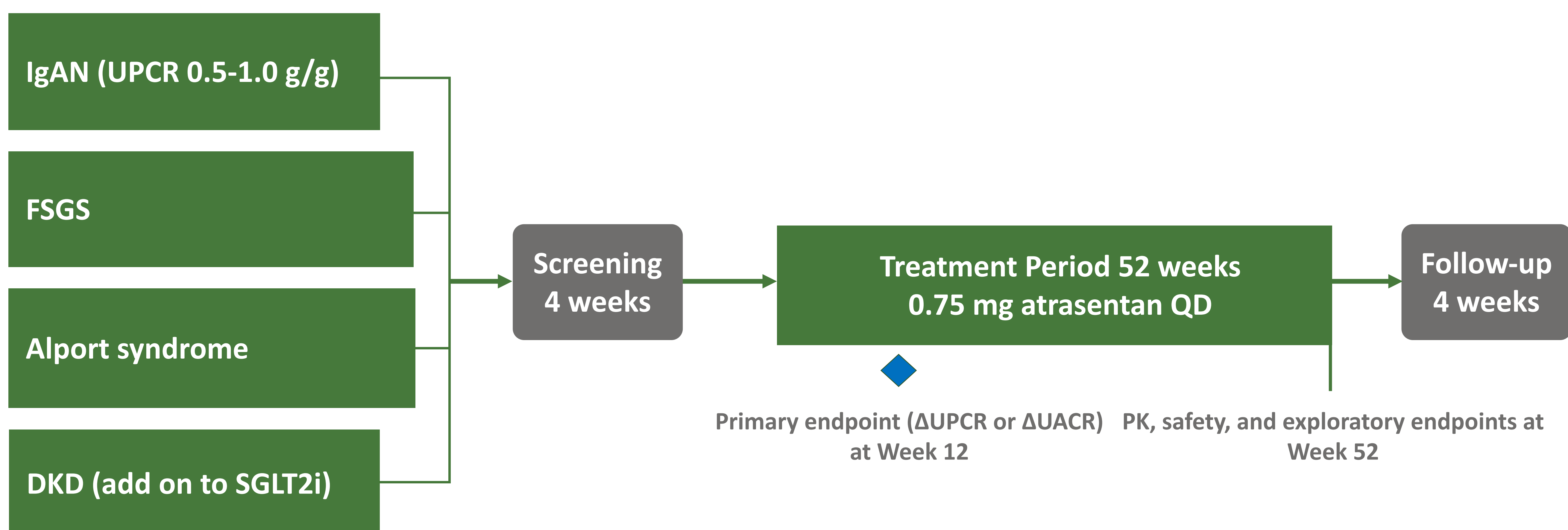
A global, phase 2, open-label basket study is planned to study efficacy and safety of atrasentan in IgAN, FSGS, Alport syndrome and DKD patients at risk of progressive loss of kidney function.

Methods

Approximately 80 patients in the United States, Australia, South Korea, Spain, Italy, and the United Kingdom with proteinuric glomerular diseases will be enrolled in a basket study to receive 0.75 mg atrasentan orally for 52 weeks. Four cohorts are planned, each consisting of 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 ration (UACR) \geq 0.5 g/g). Patients must also have an eGFR \geq 30 mL/min/1.73 m²; for DKD patients, \geq 45 mL/min/1.73 m². Participants 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 the effect of atrasentan on change in proteinuria (IgAN, FSGS, AS) or in albuminuria (DKD) from baseline at Week 12. Key exploratory objectives include changes in eGFR from Baseline to Week 52 and changes in audiology assessments in patients with Alport syndrome.

AFFINITY Study

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



- Open-label design with approximately 20 patients per cohort.
- Primarily a companion study at select ALIGN sites (see ALIGN Study Poster) with capacity to enroll to multiple cohorts.
 - 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) at 12 weeks.
- Multiple populations and indications within a single protocol to demonstrate potential for proteinuria reduction in different CKD populations of varying underlying etiologies.
- Enrollment initiation 1Q21.