The AFFINITY Trial: An Open-label Phase 2 Study of Atrasentan in Patients with Proteinuric Glomerular Diseases

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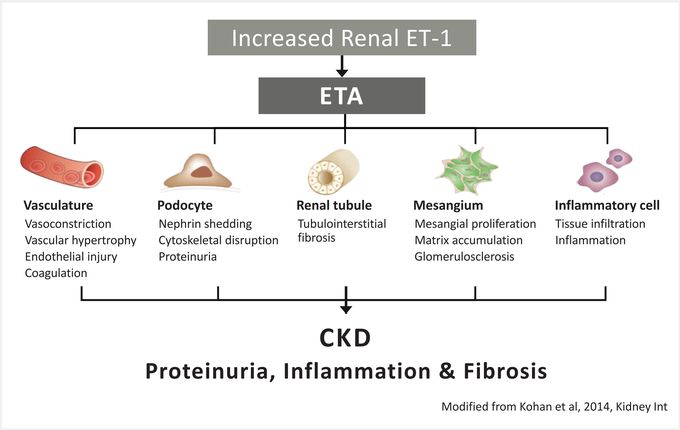
Glomerular Disease and Proteinuria

Glomerular diseases, including IgA nephropathy (IgAN), focal segmental glomerular sclerosis (FSGS), diabetic kidney disease (DKD) and Alport syndrome together are a leading cause of ESKD worldwide[1]

- Proteinuria is a predictor of disease progression and ESKD in glomerular disease[2]
- Endothelin 1 (ET-1) expression is elevated in patients with glomerular disease[3]
- Endothelin A (ET_A) receptor activation drives proteinuria, inflammation, and fibrosis[4-5]



Modified from Kohan et al, 2014, Kidney Int

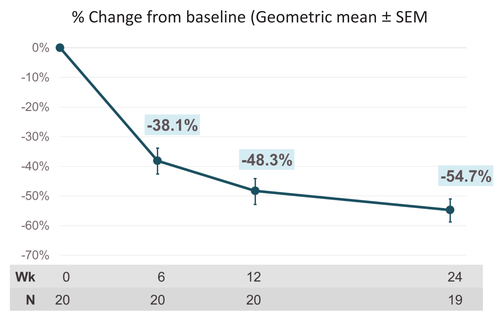
Atrasentan*

Blockade of the ET_A receptor with atrasentan, a potent and selective ET_A antagonist, represents a potential approach to reduce proteinuria and preserve kidney function in glomerular diseases

- In preclinical studies, atrasentan attenuates mesangial cell activation, glomerular and tubulointerstitial injury, and reduces proteinuria associated with IgAN [6-8]
- Atrasentan has demonstrated clinically significant and sustained proteinuria reduction with an acceptable safety profile in over 5,100 patients with DKD [9-10]

Interim results from the IgAN cohort of the ongoing AFFINITY study demonstrate atrasentan is generally well-tolerated and results in a mean 54.7% reduction in proteinuria at Week 24 (N=19; ASN 2022, TH-PO497)

% Reduction in UPCR



The AFFINITY Study

The AFFINITY study (NCT04573920) is an ongoing global phase 2 open-label basket study of safety and efficacy of atrasentan in IgAN, FSGS, Alport syndrome and DKD patients at risk of progressive loss of kidney function

Approximately 100 patients in the United States, Australia, South Korea, Spain, Italy and United Kingdom will be enrolled.

- IgAN, DKD, Alport syndrome, and FSGS (optional dose escalation) cohort enrollments are complete
- FSGS cohort (0.75 to 1.5 mg dose escalation) - **ENROLLMENT ONGOING**

		Screening, 4 weeks	Treatment, 52 weeks	Follow-up, 4 weeks
Enrollment complete	**IgA Nephropathy** *(UPCR ≥ 0.5 and < 1.0 g/g)*	N=20		
Enrollment complete	**Alport Syndrome** *(UPCR > 0.5 g/g)*	N=20	**Atrasentan 0.75 mg QD**	**Follow Up 4 weeks**
Enrollment complete	**Diabetic Kidney Disease** *(UACR > 0.5 g/g)*	N=20		
Enrollment complete	**FSGS** *(UPCR > 1.0 g/g)*	N=20	**Atrasentan** 0.75 mg QD for at least 12 weeks then *optional* dose escalation to 1.5 mg QD	**Follow Up 4 weeks**
Enrollment ongoing	**FSGS** *(UPCR > 1.0 g/g)*	N=20	**Atrasentan** 0.75 mg QD for 6 weeks then dose escalation to 1.5 mg QD	**Follow Up 4 weeks**

Key Eligibility Criteria:

- **Proteinuria must be present in all patients-** IgAN, urine protein creatinine ratio (UPCR) ≥ 0.5 and < 1.0 g/g; FSGS, UPCR > 1.0 g/g; AS, UPCR > 0.5 g/g; DKD, urine albumin creatinine ration (UACR) ≥ 0.5 g/g.
- **eGFR** ≥ 30 mL/min/1.73 m^2 in patients with IgAN, AS, or FSGS; eGFR ≥ 45 mL/min/1.73 m^2 in patients with DKD.
- Patients must be receiving maximally-tolerated **RASi** and patients with DKD must also be on **SGLT2i**.

The primary endpoint is change in proteinuria (IgAN, FSGS, AS) or albuminuria (DKD) from baseline at Week 12 for IgAN, AS and DKD, and at Week 24 post dose escalation for FSGS.

Key exploratory measures include safety, tolerability and change in eGFR from baseline to Week 52.

Reference

1. Johansen et al, 2020, Am J Kidney Dis; 2. Hunsiker et al, 1997, Kidney Int; 3. Benigni et al, 2021, Ped Nephrol; 4. Kohan et al, 2014, Kidney Int; 5. Kohan et al, 2023, KI Reports; 6. Olson et al, 2022, ERA; 7. Cox et al, 2021, Podocyte; 8. King et al, 2021, WCN; 9. de Zeeuw et al, 2014, JASN; 10. Heerspink et al, 2019, The Lancet.

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* Atrasentan is an investigational drug that has not been approved by regulatory authorities. Efficacy and safety have not been established. There is no guarantee that it will become commercially available for the use(s) under investigation.

INFO 15-TH, ASN Kidney Week, 2023, Philadelphia