A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Atrasentan in Patients with IgA Nephropathy - The ALIGN Study

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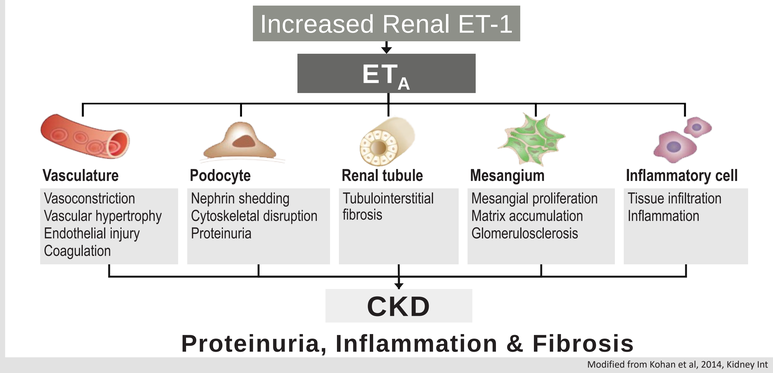
IgAN and the Endothelin Pathway

- **IgA nephropathy (IgAN) is the leading cause of primary glomerulonephritis, with a global incidence of 2.5 per 100,000 individuals per year**[1]
- **Approximately 30-45% of IgAN patients progress to end-stage kidney disease (ESKD) over a period of 20-25 years**[2-5]
- **Proteinuria is strongly associated with kidney disease progression in IgAN**[2,6-7] **and treatments that reduce proteinuria result in improved clinical outcomes in IgAN**[8-9]

Elevated kidney endothelin-1 (ET-1) expression strongly & prospectively predicts progression of IgAN 12 months following kidney biopsy[10]

Endothelin A (ET_A) receptor activation drives mesangial cell activation, kidney inflammation & fibrosis, and proteinuria, all hallmarks of IgAN[11-12]

Kidney ET-1 & ET_A receptor levels are elevated in proteinuric patients with IgAN[13-14]



Modified from Kohan et al, 2014, Kidney Int

Atrasentan*

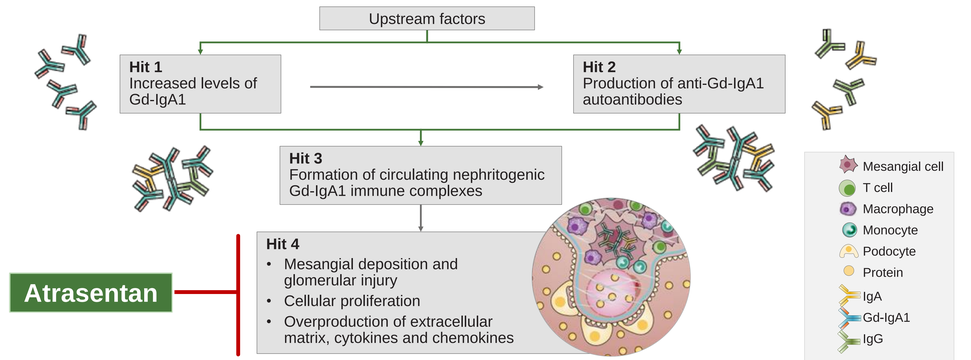
Blockade of the ET_A receptor with atrasentan, a potent and selective ET_A antagonist, represents a potential approach to reduce proteinuria and preserve kidney function in IgAN[15]

In preclinical studies, atrasentan attenuates mesangial cell activation, glomerular and tubulointerstitial injury, and reduces proteinuria associated with IgAN[16-18]

Atrasentan has demonstrated clinically significant and sustained proteinuria reduction with an acceptable safety profile in over 5,100 patients with DKD [19-20]

Interim results from the IgAN cohort of the ongoing AFFINITY study (NCT04573920) demonstrate that atrasentan is generally well-tolerated and results in a mean 54.7% reduction in proteinuria at Week 24 (N=19; ASN 2022, TH-PO497)

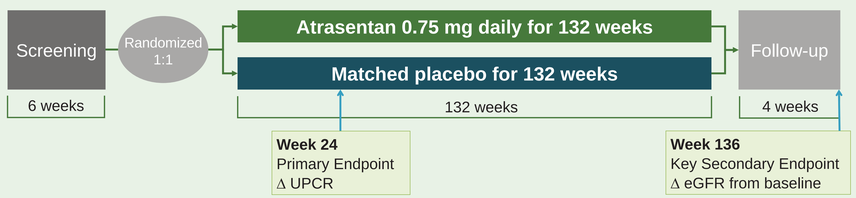
IgA Nephropathy Disease Pathophysiology



Modified from Lai et al, 2016, Nat Rev Dis Primers

The ALIGN Study

The ongoing ALIGN study (NCT04573478) is a global phase 3, randomized, double-blind, placebo-controlled study of atrasentan in patients with IgAN who are at high risk of kidney function loss



Approximately 320 patients will be enrolled across North America, South America, Europe, and Asia-Pacific

Major inclusion criteria:

- **Biopsy-proven IgAN** with total protein excretion ≥1 g per 24 hrs and eGFR ≥30 mL/min/1.73 m^2
- Receiving max-tolerated and optimized dose of RASi for ≥12 weeks prior to screening; a limited number of patients (up to 5%) that are unable to tolerate RASi therapy may be enrolled
- **An additional stratum of up to 64 patients receiving a stable dose of SGLT2i for at least 12 weeks will be enrolled**

The primary endpoint is change in proteinuria from baseline at Week 24.

Key Secondary endpoint is change in eGFR from baseline at week 136.

Additional endpoints include safety and tolerability, and quality of life.

Reference

1. Mcgrogan et al, 2011, NDT; 2. Reich et al, 2007, JASN; 3. Moriyama et al, 2014, PLOS ONE; 4. Rauen et al, 2020, Kidney Int; 5. Hastings et al, 2018, Kidney Int Rep; 6. Thompson et al, 2019, CJASN; 7. Barbour et al, 2019, JAMA Int Med; 8. Inker et al, 2016 AJKD; 9. Inker et al, 2019, CJASN; 10. Tycova et al, 2018, Physiol Res; 11. Kohan et al, 2014, Kidney Int; 12. Raina et al, 2020, Kidney Dis; 13. Lehrke et al, 2001, JASN; 14. Zanatta et al, 2012, Renal Failure; 15. Wessale et al, 2002, Clin Sci; 16. Olson et al, 2022, ERA; 17. Cox et al, 2021, Podocyte; 18. King et al, 2021, WCN; 19. de Zeeuw et al, 2014, JASN; 20. Heerspink et al, 2019, 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.