The ASSIST Trial: A Randomized, Double-blind, Placebo-controlled, Crossover Study of Atrasentan in Patients with IgA Nephropathy on SGLT2i

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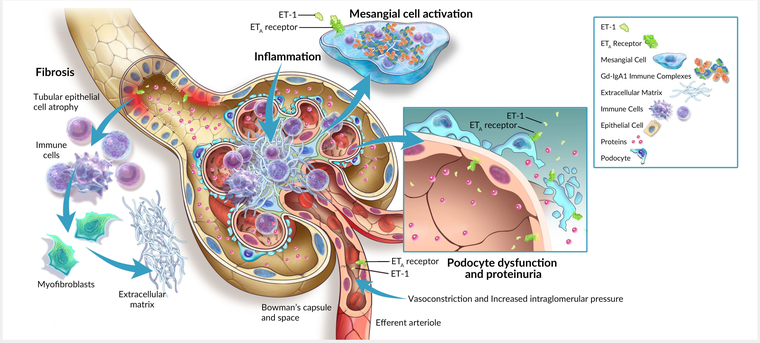
Background

Glomerular Disease and Proteinuria

- IgA nephropathy (IgAN) is the leading cause of primary glomerulonephritis, with approximately 30-45% of IgAN patients progressing to ESKD over a period of 20-25 years[1-4]
- Proteinuria is the strongest predictor of disease progression in IgAN[1,5-6]
- Endothelin A (ETA) receptor activation may contribute to mesangial cell activation, proteinuria, kidney inflammation and fibrosis in IgAN (Figure)[7,8]



Atrasentan* and SGLT2i

Atrasentan, a potent and selective ET_A antagonist, has potential to reduce proteinuria and preserve kidney function in IgAN.

- Interim results of a phase 2, open-label study in patients with IgAN (AFFINITY, NCT04573920) demonstrated that atrasentan was well tolerated and resulted in clinically meaningful and sustained proteinuria reductions in patients receiving a maximally tolerated and optimized dose of a RAS inhibitor[9]
- Sodium glucose cotransporter-2 inhibitors (SGLT2is) are approved for use in adults with CKD at risk of kidney disease progression, including IgAN[10]
- In a post-hoc analysis of the global phase 3 SONAR study in patients with type 2 diabetes and CKD, 6-week treatment with atrasentan and SGLT2i in a small number of patients (n=14) further decreased albuminuria and decreased body weight, a surrogate for fluid retention, vs. atrasentan alone [11]

References

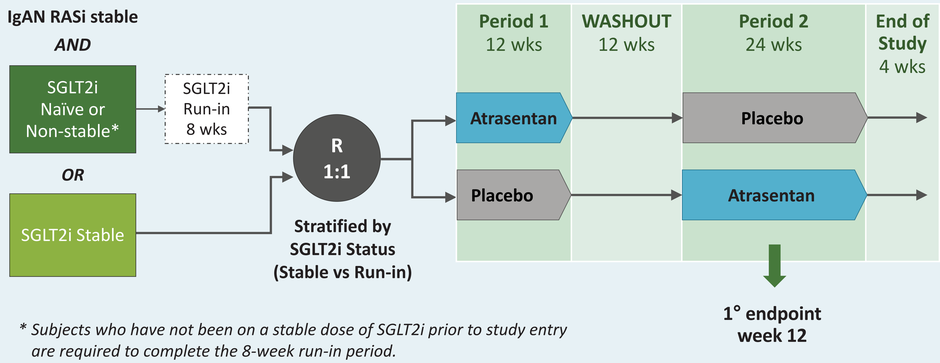
1. Reich et al, 2007, JASN; 2. Moriyama et al, 2014, PLOS ONE; 3. Rauen et al, 2020, Kidney Int; 4. Hastings et al, 2018, Kidney Int Rep; 5. Thompson et al, 2019, CJASN; 6. Barbour et al, 2019, JAMA Int Med; 7. Kohan et al, 2014, Kidney Int; 8. Raina et al, 2020, Kidney Dis; 9. Rastogi et al, 2022, ASN Kidney Week, TH-PO497; 10. Wheeler et al, 2021, Kidney Int;11. Heerspink et al, 2021, Kidney Intl.

ASSIST Study Design

ASSIST™

Study Objective:

ASSIST™ (NCT05834738) is a randomized, double-blind, placebo-controlled, crossover study to evaluate the safety and efficacy of atrasentan vs. placebo in adults with IgAN on stable SGLT2i and RASi with persistent proteinuria. Approximately 52 patients will be enrolled.



** Subjects who have not been on a stable dose of SGLT2i prior to study entry are required to complete the 8-week run-in period.*

Study Endpoints:

- **Primary:** Change in proteinuria (UPCR from a 24-hour urine collection) from baseline to week 12
- **Key secondary:** In Treatment Period 2, the change in proteinuria (UPCR from a 24 hr urine collection) from baseline to week 24
- **Safety:** Type, incidence, severity, and relatedness of adverse events (AEs) and serious AEs
- **Exploratory:** In Treatment Period 2, change in eGFR from baseline to week 24

Key inclusion criteria

All patients	✓ Adults with biopsy-proven IgAN, not due to secondary causes ✓ Receiving max tolerated and stable RASi ≥ 12 weeks prior to screening ✓ eGFR ≥ 30 mL/min/1.73 m^2 (CKD-EPI) at screening
SGLT2i stable	✓ Receiving SGLT2i at stable dose ≥ 8 weeks prior to screening ✓ 24-hour total urine protein > 0.5 g/d at screening
SGLT2i naïve or non-stable	✓ 24-hour total urine protein > 0.85 g/d at screening ✓ Complete 8-week run-in period on a stable and well tolerated dose of an SGLT2i ✓ After run-in: • 24-hour total urine protein > 0.5 g/d confirmed at end of run-in • eGFR of ≥ 30 mL/min/1.73 m^2 (CKD-EPI) at end of run-in

Summary

- Atrasentan, a potent and selective ETA antagonist, has potential to reduce proteinuria and preserve kidney function in IgAN
- The ASSIST crossover study will evaluate the safety and efficacy of atrasentan in combination with SGLT2i in patients with IgAN with persistent proteinuria despite maximized RASi

The ASSIST study is currently enrolling

For more information, scan QR or visit
https://clinicaltrials.gov/ct2/show/NCT05834738

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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.

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