#4341

ASSIST STUDY DESIGN: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSSOVER STUDY OF ATRASENTAN IN PATIENTS WITH IGA NEPHROPATHY (IGAN) ON SGLT2I

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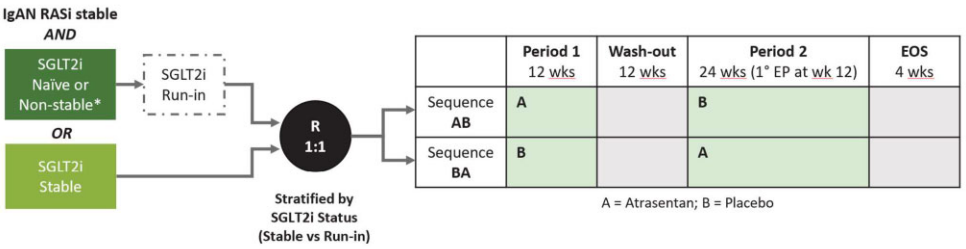
Background and Aims: IgA nephropathy (IgAN) is the leading cause of primary glomerulonephritis. Approximately 30-45% of IgAN patients progress to ESKD over a period of 20-25 years and proteinuria is the strongest predictor of disease progression. Endothelin A (ET_A) receptor activation drives proteinuria, kidney inflammation and fibrosis. 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 (RASi; Kim *et al.* 2022, ASN Kidney Week FC052). Sodium glucose cotransporter-2 inhibitors (SGLT2is) are approved for use in adults with CKD at risk of kidney disease progression. In a post-hoc analysis of a global phase 3 study in patients with type 2 diabetes and CKD (SONAR), 6 week treatment with SGLT2i and atrasentan (n = 14) resulted in greater reductions in albuminuria (change in UACR from baseline −54.7%, 95%CI −64.6 to −42.0) compared to atrasentan alone (change in UACR from baseline −37.6%, 95%CI −45.9 to −28.0), suggesting independent and additive effects of both drug classes (Heerspink *et al.* 2021, Kidney Intl). The ASSIST study will evaluate the safety and efficacy of atrasentan vs. placebo in adults with IgAN and persistent proteinuria while on stable background SGLT2i and RASi therapy.

Methods: The ASSIST trial is a randomized, double-blind, placebo-controlled, crossover clinical trial. Approximately 52 patients with biopsy-proven IgAN and eGFR ≥ 30 mL/min/1.73 m^2 (CKD-epi) who are receiving maximally tolerated RASi for at least 12 weeks prior to screening will be enrolled. Patients on a stable dose of SGLT2i prior to screening (SGLT2i stable) must have total urine protein of >0.5 grams/day at screening. Patients who are not currently on SGLT2i or are not on a stable dose of SGLT2i must have a total urine protein of >0.85 grams/day at screening and enter a run-in period during which they receive SGLT2i for 8 weeks (SGLT2i run-in), after which they must have a total urine protein of >0.5 grams/day confirmed at the Week-1 visit (Figure). Choice of SGLT2i will be at the discretion of the principal investigator and per local treatment standards. Thereafter, all eligible patients will be randomized 1:1 to sequence AB or sequence BA in which they will receive 0.75 mg atrasentan once daily (QD) during one period and placebo during the other period. Randomization will be stratified by SGLT2i status (stable vs run-in). All subjects will enter Treatment Period 1 for 12 weeks, followed by a 12-week washout period, and then Treatment Period 2 for 24 weeks. Following the end of treatment, patients will have follow-up evaluations for safety approximately 4 weeks after the end of treatment. Fifty-two subjects will provide approximately 83% power using a two-sided pairwise test (α 0.05) to detect a treatment effect of at least 0.288 in natural log transformed UPCR (25% reduction) between atrasentan and placebo.

Results: Primary and secondary endpoints are change in proteinuria (UPCR from 24-hr collection) from baseline to week 12 and week 24, respectively. Type, incidence, severity, seriousness, and relatedness of adverse events will be evaluated. Change in eGFR from baseline to week 24 in Treatment Period 2 will be evaluated as an exploratory endpoint.

Conclusion: Atrasentan is a potent and selective ETA antagonist. Interim results from the AFFINITY Phase 2 open-label study demonstrated that atrasentan resulted in sustained, clinically meaningful reductions in proteinuria in patients with IgAN. The phase 2 ASSIST study will examine the effects of atrasentan in combination with SGLT2i in patients with IgAN who are also receiving maximally tolerated RASi.



*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.

EOS, end of study; IgAN, immunoglobulin A nephropathy; EP, endpoint; R, randomization; RASi, renin-angiotensin system inhibitor; SGLT2i, sodium-glucose co-transporter 2 inhibitor

Figure 1: