WCN 2024 ASSIST Trial-in-Progress

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

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Introduction:

IgA nephropathy (IgAN) is the leading cause of primary glomerulonephritis and has limited treatment options. Endothelin A (ET_A) receptor activation drives increase in proteinuria, kidney inflammation and fibrosis. In interim results of a phase 2, open-label study in patients with IgAN (AFFINITY), atrasentan, a potent and selective ET_A antagonist, was well tolerated and resulted in clinically meaningful proteinuria reduction. Meanwhile, in a post-hoc analysis in patients with type 2 diabetes and CKD (SONAR), treatment with sodium glucose cotransporter-2 inhibitors (SGLT2i) and atrasentan resulted in greater reductions in albuminuria compared to atrasentan alone (n=14). The ASSIST trial will evaluate the safety and efficacy of atrasentan vs. placebo in adults with IgAN and persistent proteinuria while on stable background of SGLT2i and RASi.

Methods:

The ASSIST trial (NCT05834738) is a randomized, double-blind, placebo-controlled crossover study that will enroll 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. 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. 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 completion of Treatment Period 2, patients will have follow-up safety evaluations at approximately 4 weeks.

Results:
The primary endpoint is change in proteinuria (UPCR from 24-hr collection) from baseline to week 12 in Treatment Period 1 and the secondary endpoint is change in proteinuria week 24 in Treatment Period 2. 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 ET_A 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. This trial design has been previously presented at ERA 2023, Milan, and ASN 2023, Philadelphia.

Category: The Smart Kidney: Genetics, precision medicine, machine learning/AI, rare/orphan kidney diseases

Subcategory: Clinical glomerulonephritis

Keywords: IgA nephropathy, glomerulonephritis, clinical trial