Atrasentan for the Treatment of IgA Nephropathy: Interim Results from the AFFINITY Study

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Background/Methods

IgA Nephropathy (IgAN)
- IgA is the leading cause of primary glomerulonephritis, with a global incidence of 2.5 per 100,000 individuals per year
- Approximately 30-45% of IgAN patients progress to end-stage kidney disease (ESKD) over a period of 20-25 years
- Proximal tubulopathy is strongly associated with kidney disease progression in IgAN and treatments that reduce proteinuria result in improved clinical outcomes in IgAN

Endothelin System Activation in IgAN
- Endothelin (ET-1) is a key contributor to progression of IgA nephropathy
- Elevated kidney ET-1 expression strongly & prospectively predicts progression of IgA nephropathy 12 months following kidney biopsy
- Endothelin A (ET-A) receptor activation drives mesangial cell activation, kidney inflammation & fibrosis, and proteinuria, all hallmarks of IgAN

AFFINITY Study Design
- AFFINITY is a global, phase 2, open label basket study to assess the efficacy and safety of atrasentan in patients with proteinuric glomerular diseases (IgAN, focal segmental glomerulosclerosis (FSGS), APLS, and DKD) at risk of progressive kidney function loss

Atrasentan- has potential to treat IgAN patients at high risk of progression
- Atrasentan is a potent and highly selective endothelin receptor antagonist (0.75 mg, 1.5 mg, or 3.0 mg) with 180-fold selectivity over ET B (EJ 3.34±0.65)
- Atrasentan has previously demonstrated clinically significant and sustained proteinuria reduction with an acceptable safety profile in over 5,100 patients with diabetic kidney disease (DKD)
- In preclinical studies, atrasentan attenuates mesangial cell activation, glomerular and tubulointerstitial injury, and reduces proteinuria associated with IgAN

Baseline and Safety

AFFINITY IgAN Cohort
- The AFFINITY IgAN cohort enrolled 20 patients with biopsy-confirmed IgAN
- All patients received concurrent, maximally tolerated and optimized dose of a RAS inhibitor for ≥ 12 weeks prior to study entry and throughout the study period
- 70% of patients had baseline total urinal protein >1 g/day despite optimized RASI treatment, representing an IgAN population at high risk for progression
- Mean treatment duration was 45 weeks (range 13-53 weeks) as of data cut-off October 19, 2022

No Evidence of Significant Fluid Retention
- No increase in mean body weight
- No significant elevation in BNP (median change of 2.3 pg/ml at week 12)
- No mean change in systolic or diastolic BP
- Minimal mean change in eGFR (0.15 ± 0.23 ml/min/1.73 m² averaged across Weeks 2 and 6)

Results

Proteinuria Reduction in Patients with IgAN
- Treatment with atrasentan results in a durable and clinically meaningful proteinuria reduction in patients with IgAN receiving optimized standard-of-care
- 76% of patients achieved >40% reduction in proteinuria at Week 24

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Safety and Tolerability
- Atrasentan was generally well tolerated with treatment-related adverse events (AEs)
- One treatment-emergent AE (headache) led to study withdrawal

Summary/Conclusion

The AFFINITY IgAN Cohort enrolled 20 patients with IgAN at high risk for kidney disease progression
- Treatment with atrasentan resulted in clinically meaningful reductions in proteinuria at weeks 6, 12 and 24
- There were no meaningful changes in blood pressure nor acute eGFR changes, suggesting proteinuria reductions were not primarily due to hemodynamic effects of atrasentan
- Atrasentan was generally well-tolerated with no treatment-related SAEs
- There was no increase in BNP or mean body weight, suggesting minimal fluid retention

This analysis demonstrates that treatment with atrasentan results in clinically meaningful proteinuria reductions in patients with IgAN who remain at risk for progression with residual proteinuria despite optimized standard-of-care treatment.

Ongoing ALIGN phase 3 trial of atrasentan in patients with IgAN
- The ALIGN study (NCT04573920) is a currently enrolling/opening 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

Key Study Endpoints:
- The primary endpoint is change in proteinuria from baseline to Week 24
- The key secondary endpoint is change in eGFR from baseline at Week 12
- Additional endpoints include safety, tolerability, and quality of life

References

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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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