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

Sung Gyun Kim[1], Lesley A. Inker[2], David K. Packham[3], Dwarakanathan Ranganathan[4], Anjay Rastogi[5], Michelle N. Rheault[6], Mark Vishnepolsky[7], Khushboo Sheth[8], Todd DeVries[8], Marianne Camargo[8], Andrew J. King[8], Charlotte Jones-Burton[8], Seung Hyeok Han[9]

1. Hallym University Sacred Heart Hospital, Anyang, Gyeonggi-do, South Korea; 2. Tufts Medical Center, Boston, MA, United States; 3. Melbourne Renal Research Group, Reservoir, VIC, Australia; 4. Royal Brisbane and Women's Hospital, Herston, QLD, Australia; 5. University of California Los Angeles, Los Angeles, CA, United States; 6. University of Minnesota Division of Pediatric Nephrology, Minneapolis, MN, United States; 7. Kidney Specialists of Southern Nevada, Las Vegas, NV, United States; 8. Chinook Therapeutics Inc, Seattle, WA, United States; 9. Severance Hospital, Yonsei University Health System, Seoul, South Korea

Background/Methods

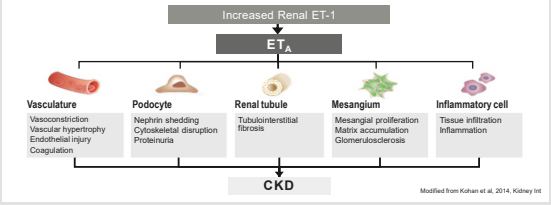
IgA Nephropathy (IgAN)

- 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]

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 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]

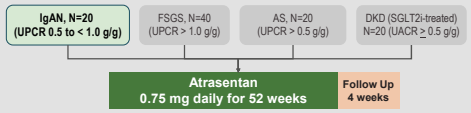


Atrasentan* has potential to treat IgAN patients at high risk of progression

- Atrasentan is a potent and highly-selective endothelin receptor A antagonist (Ki = 0.034nM) with >1,800-fold selectivity over ETB (Ki = 63.3nM)[15]
- 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)[16-17]
- In preclinical studies, atrasentan attenuates mesangial cell activation, glomerular and tubulointerstitial injury, and reduces proteinuria associated with IgAN [18-21]

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], Alport syndrome [AS], and DKD) at risk of progressive kidney function loss (NCT04573920)



Key Eligibility Criteria, IgAN Cohort

- Biopsy-proven IgAN
- Maximally-tolerated and optimized dose of a RAS inhibitor (RASi) for ≥ 12 weeks prior to screening
- UPCR of 0.5 to < 1.0 g/g (56.5 mg/mmol to <113 mg/mmol) based on first morning void urine collected at screening
- eGFR ≥ 30 mL/min/1.73 m^2

Key Study Endpoints

- Change from baseline at week 12 in UPCR, based on average of two 24-hour collections
- Analysis based on an MMRM model of change from baseline in UPCR
- Adverse Event (AE) type, incidence, severity, seriousness and relatedness

Baseline and Safety

AFFINITY IgAN Cohort

- The AFFINITY IgAN cohort enrolled 20 patients with biopsy-confirmed IgAN
- All patients received concurrent, max-tolerated and optimized RASi at least 12 weeks prior to study and throughout the study period
- 70% of patients had baseline total urine 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

DEMOGRAPHICS, N=20	
Age, years, *median (Q1,Q3)*	45 (35, 58)
Women, *n (%)*	10 (50)
Race, *n (%)*, **Asian**	9 (45)
White	9 (45)
Other	2 (10)
BASELINE CHARACTERISTICS	***Median (Q1, Q3)***
Time from biopsy, years	3.9 (0.9, 11.8)
Blood pressure (mmHg) – Systolic	128 (116, 132)
– Diastolic	82 (77, 86)
BMI	26.2 (24.8, 29.2)
Brain Natriuretic Peptide (pg/mL)	12.5 (8.8, 42.0)
UPCR (g/g), First morning void at screening	0.6 (0.5, 0.7)
24-hour UPCR (g/g)	0.8 (0.7, 1.1)
24-hour urine protein excretion (g/day)	1.2 (0.9, 1.5)
Urine protein excretion (g/day) ≥ 1, n (%)	14 (70)
eGFR (mL/min/1.73 m^2) §	46 (37, 74)
Concurrent RASi, n (%)	20 (100)
ACEi	8 (40)
ARB	12 (60)

§eGFR by CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration

Safety and Tolerability

- Atrasentan was generally well-tolerated with no treatment-related severe AEs to date
- One treatment-emergent AE (headache) led to study withdrawal

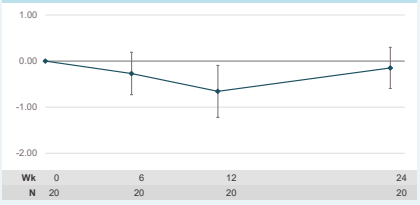
AE Category (N=20)		n (%)
Treatment emergent AEs (TEAEs), Severe AEs	Subjects with any TEAE	16 (80)
	Any TEAE occurring in N>1 subjects COVID-19 Dizziness Peripheral edema Headache	7 (35) 3 (15) 2 (10) 2 (10)
	Any Moderate TEAE	6 (30)
	Any Severe TEAE	0 (0)
	TEAE leading to discontinuation (headache)	1 (5)
	Serious AE (traffic accident unrelated to study drug)	1 (5)
Treatment-related AEs	Any treatment-related AE	5 (25)
	Moderate related AEs Headache Creatinine increase/Renal impairment Peripheral edema	3 (15) 1 1 1

Data cut-off Oct. 19, 2022

No Evidence of Significant Fluid Retention

- No increase in mean body weight
- No significant elevation in BNP (median change of 2.9 pg/mL at week 12)
- No meaningful change in systolic or diastolic BP
- Minimal acute change in eGFR (0.15 mL/min/1.73 m^2 averaged across Weeks 2 and 6)

Body Weight
Mean Change from Baseline ± SE (kg)



Data cut-off Oct. 19, 2022

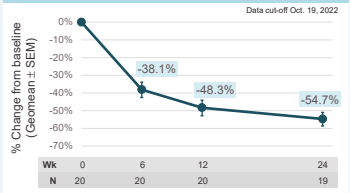
Results

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

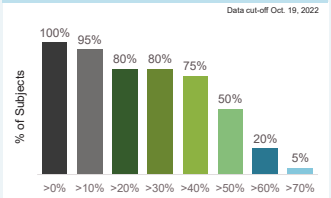
- 79% of patients achieved >40% reduction in proteinuria at Week 24

% Reduction in UPCR

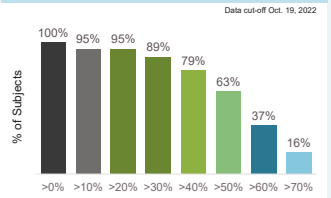


Median (range) baseline protein excretion: 1.2 (0.9, 1.5) g/day

Week 12 (n=20)
UPCR Cumulative % Reduction



Week 24 (n=19)
UPCR Cumulative % Reduction



Conclusions

- In this Phase 2 study of 20 patients with biopsy-proven IgAN, 70% of patients had baseline total urine protein >1 g/day despite optimized SOC treatment, representing an IgAN population 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 bodyweight, 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 (NCT04573478) is a currently enrolling/ongoing 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.

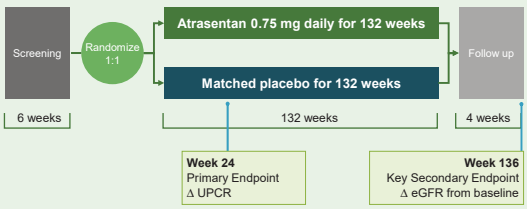
Major Inclusion Criteria

- 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 at least 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**

Key Study Endpoints

Non-SGLT2i Stratum-

- The primary endpoint is change in proteinuria from baseline at Week 24
- The key secondary endpoint is change in eGFR from baseline at Week 136
- Additional endpoints include safety, tolerability, and quality of life



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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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