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

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Disclosures for Presenting Author:

<table>
<thead>
<tr>
<th>Current Employer:</th>
<th>Concord Repatriation General Hospital, Sydney, Australia</th>
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<tbody>
<tr>
<td>Honoraria:</td>
<td>Baxter, Amgen, AstraZeneca, CSL Behring, Dimerix, Otsuka, Chinook and Travere</td>
</tr>
<tr>
<td>Scientific Advisor or Membership:</td>
<td>Member of the Steering Committee for PROTECT, DUPLEX and VISIONARY trials</td>
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Previous Employer, the George Institute for Global Health, holds research contracts for trials in cardiovascular and/or kidney disease in Asia Pacific region
IgA Nephropathy (IgAN): A Potentially Progressive, Chronic Glomerular Disease with Limited Treatment Options

#1 IgAN is the most common primary glomerulonephritis globally, though it is considered a rare disease

ESKD 30-45%

End-stage kidney disease (ESKD) is developed by about 30-45% of IgAN patients over a period of 20-25 years

Limited treatment options for high-risk patients:

- RAS inhibition (ACEi/ARB) is frontline (KDIGO 1B)
- Steroids & immunosuppressive agents: inconsistent therapeutic benefit and accompanied by significant side effects (KDIGO 2B); Tarpeyo (budesonide) recently approved
- DAPA-CKD: suggests benefit of SGLT2i in non-diabetic CKD, including IgAN

Endothelin System Activation in IgAN Disease Progression

ET<sub>A</sub> activation reported to result in:

- Mesangial cell activation
- Proteinuria
- Kidney inflammation & fibrosis

... all hallmark characteristics of IgAN

Increased Renal ET-1

ET<sub>A</sub>

Vasculature
- Vasoconstriction
- Vascular hypertrophy
- Endothelial injury
- Coagulation

Podocyte
- Nephrin shedding
- Cytoskeletal disruption
- Proteinuria

Renal tubule
- Tubulointerstitial fibrosis

Mesangium
- Mesangial proliferation
- Matrix accumulation
- Glomerulosclerosis

Inflammatory cell
- Tissue infiltration
- Inflammation

CKD

Elevated kidney ET-1 expression strongly & prospectively predicted progression of IgAN, 12 months following kidney biopsy

Intense glomerular and TI ET-1 expression in IgAN patients with significant proteinuria

Blockade of the ET<sub>A</sub> receptor with potent and selective ET<sub>A</sub> antagonist atrasentan, represents a potential approach to treat IgAN patients at high risk of progression (Hit 4)

AFFINITY Study Design: Atrasentan in Patients With Proteinuric Glomerular Diseases

**Study Objective**

AFFINITY is a global, phase 2, open label basket study to assess the efficacy and safety of atrasentan in patients with proteinuric glomerular diseases at risk of progressive kidney function loss.

**Screening**

- IgA Nephropathy (UPCR 0.5 to < 1.0 g/g) \(N=20\)
- FSGS (UPCR > 1.5 g/g) \(N=20\)
- Alport Syndrome (UPCR > 0.5 g/g) \(N=20\)
- Diabetic Kidney Disease (UACR > 0.5 g/g) \(N=20\)

**Atrasentan**

0.75 mg daily for 52 weeks

**Follow Up**

4 weeks

* Stable RASi for all cohorts (in addition to stable SGLT2i for diabetic kidney disease).

All cohorts eGFR ≥ 30 ml/min/1.73m², except for DKD ≥ 45 ml/min/1.73m²

AFFINITY Study Protocol; ClinicalTrials.gov Identifier: NCT04573920
### Key Eligibility Criteria

**Biopsy-proven IgAN** that, in the opinion of the Investigator, is not due to secondary causes*

- Receiving a maximally tolerated and optimized dose of a **RAS inhibitor** that has been stable for at least 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 m²**

### Key Study Endpoints

**Primary Endpoint**

- **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

**AE type, incidence, severity, seriousness and relatedness**

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* Biopsy could have occurred at any point in time prior to study.

AE, adverse event; MMRM, mixed-effects model repeated measures (fixed effects of visit and baseline in UPCR)
<table>
<thead>
<tr>
<th>Demographics (n=20)</th>
<th>Median (Q1, Q3)</th>
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<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>45 (35, 58)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td>10 (50)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td>9 (45)</td>
</tr>
<tr>
<td><strong>Asian</strong></td>
<td>9 (45)</td>
</tr>
<tr>
<td><strong>White</strong></td>
<td>2 (10)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>26.2 (24.8, 29.2)</td>
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<table>
<thead>
<tr>
<th>Baseline Characteristics (cont)</th>
<th>Median (Q1, Q3)</th>
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<tbody>
<tr>
<td><strong>UPCR, First morning void at screening (g/g)</strong></td>
<td>0.63 (0.54, 0.70)</td>
</tr>
<tr>
<td><strong>24-hour UPCR (g/g)</strong></td>
<td>0.80 (0.73, 1.10)</td>
</tr>
<tr>
<td><strong>24-hour urine protein excretion (g/day)</strong></td>
<td>1.17 (0.85, 1.46)</td>
</tr>
<tr>
<td><strong>Urine protein excretion (g/day) ≥ 1, n (%)</strong></td>
<td>14 (70)</td>
</tr>
<tr>
<td><strong>eGFR (mL/min/1.73 m²)</strong></td>
<td>46 (37, 74)</td>
</tr>
<tr>
<td><strong>Concurrent RASi, n (%)</strong></td>
<td>20 (100)</td>
</tr>
<tr>
<td><strong>ACEi</strong></td>
<td>8 (40)</td>
</tr>
<tr>
<td><strong>ARB</strong></td>
<td>12 (60)</td>
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* eGFR by CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration
Safety and Tolerability

To date*, atrasentan has been well-tolerated in patients with IgAN (n=20)

18/20 patients remain on treatment, with time on treatment ranging from 6-52 weeks. One patient discontinued treatment and one patient has completed 52 weeks.

<table>
<thead>
<tr>
<th>AE Category</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td>Subjects with any TEAE</td>
<td>16 (80)</td>
</tr>
<tr>
<td>Any TEAE occurring in N&gt;1 subjects</td>
<td></td>
</tr>
<tr>
<td>COVID-19</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Any Moderate TEAE</td>
<td>6 (30)</td>
</tr>
<tr>
<td>Any Severe TEAE</td>
<td>0 (0)</td>
</tr>
<tr>
<td>TEAE leading to discontinuation (headache)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>SAE (traffic accident unrelated to study drug)</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AE Category</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-related AE</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Moderate related AE</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
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<tr>
<td>Creatinine increase</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>1</td>
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</tbody>
</table>

*Data cut-off: April 22, 2022. AE, adverse event; TEAE, treatment-emergent adverse event; SAE, serious adverse event.

➢ No SAEs related to study drug to date
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 m² averaged across Weeks 2 and 6)
Atrasentan Provides Clinically Meaningful Proteinuria Reduction in Patients with IgAN Receiving Optimized SOC

% Reduction in UPCR*

*Results plotted are based on the least squares mean +/- SE of change from baseline on natural log scale from the MMRM back-transformed to a percent reduction from baseline scale.
Atrasentan Provides Clinically Meaningful Proteinuria Reduction in Patients with IgAN Receiving Optimized SOC

➢ 91% of patients achieved >40% reduction in proteinuria at Week 24
Treatment with Atrasentan Provides Clinically Meaningful Proteinuria Reduction and is Well-tolerated in Patients with IgAN

Interim AFFINITY IgAN data:

- In this Phase II study with 20 patients, 70% of patients had baseline total urine protein >1g/day despite optimized SOC treatment, representing an IgAN population at high risk for 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 and acute eGFR, suggesting proteinuria reductions were not primarily due to hemodynamic effects of atrasentan
- Generally well-tolerated with no treatment-related SAEs
- There was no increase in BNP and mean bodyweight, suggesting minimal fluid retention

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

ALIGN phase 3 trial of atrasentan in patients with IgAN is currently enrolling (NCT04573478)

Inclusion:
- eGFR ≥ 30 mL/min/1.73 m²
- Total urine protein ≥ 1 g/day based on 24-hour urine collection at screening