Selective ET<sub>2</sub> Antagonist Atrasentan, Rapidly Reduces Albuminuria and Downregulates Intra-renal Pro-Inflammatory and Pro-Fibrotic Transcriptional Networks in the gddY Mouse Model of Spontaneous IgA Nephropathy

Andrew King<sup>1</sup>, Renata Oballa<sup>1</sup>, Marvin Gunawan<sup>1</sup>, Jennifer Cox<sup>1</sup>, Eric Olson<sup>1</sup>, Joyce Wu<sup>1</sup>, Oliver Chong<sup>1</sup>, Jayakumar Surendradoss<sup>1</sup>, Jeff Lester<sup>1</sup>, Charles Nieh<sup>1</sup>, Toshiki Kano<sup>2</sup> and Yusuke Suzuki<sup>2</sup>

<sup>1</sup>Chinook Therapeutics, <sup>2</sup>Gunma University

Background

Endothelin pathway activation, which has been observed in kidney biopsies from IgA nephropathy (IgAN) patients, may be an important driver of disease progression by activating proinflammatory inflammation and fibrosis via ET<sub>2</sub> receptor activation.<sup>1</sup> Atrasentan is a potent and selective ET<sub>2</sub> antagonist which has demonstrated rapid and sustained reductions in proteinuria, preservation of kidney function and improved kidney outcomes in diabetic kidney disease patients.<sup>6</sup> However, the effects of atrasentan have not been previously investigated in IgAN. The objective of this study was to evaluate the effect of short-term treatment of varying doses of atrasentan in the gddY mouse model of spontaneous IgAN with a focus on dynamic changes in the intra-renal transcriptional profile.

The gddY mouse is a spontaneous model of early-onset IgAN characterized by IgA immune complex deposition in the mesangium of the kidney, leading to significant proteinuria, glomerular hypercellularity, mesangiotrophic mesangial lesions, glomerulosclerosis and reduced kidney function, all hallmarks of human IgAN.<sup>2</sup>

Methods

1. Administered atrasentan doses
   - Atrasentan dose = [atrasentan] x 24 hour water consumption / body weight
   - The mean daily dose of atrasentan administered was 7.8, 16.0 and 29.0 mg/kg/day, in close approximation to the targeted doses of 10, 20 and 30 mg/kg/day respectively

2. Albuminuria
   - At baseline, the gddY mice had substantial albuminuria, which was well matched across treatment groups
   - Atrasentan reduced UACR from baseline by 28 ± 4%, 62 ± 8% and 63 ± 6% at 10, 20 and 30 mg/kg/day, respectively

3. Plasma atrasentan concentrations
   - Few (1) [atrasentan] plasma concentrations covered the ET<sub>2</sub> Ki<sub>1</sub> and were highly selective over ET<sub>1</sub> consistent with human exposures (0.75 mg/dL)

Table 1. Atrasentan plasma concentrations at baseline and following treatment with varying doses of atrasentan in gddY mice:

<table>
<thead>
<tr>
<th>Dose (mg/kg/day)</th>
<th>Baseline (nmol/L)</th>
<th>Day 3 (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>7.8</td>
<td>7.6</td>
</tr>
<tr>
<td>20</td>
<td>39</td>
<td>2.9</td>
</tr>
<tr>
<td>30</td>
<td>99</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>0.0133</td>
<td>704</td>
</tr>
</tbody>
</table>

Results

1. Administered atrasentan doses
   - Atrasentan dose = [atrasentan] x 24 hour water consumption / body weight
   - The mean daily dose of atrasentan administered was 7.8, 16.0 and 29.0 mg/kg/day, in close approximation to the targeted doses of 10, 20 and 30 mg/kg/day respectively

2. Albuminuria
   - At baseline, the gddY mice had substantial albuminuria, which was well matched across treatment groups
   - Atrasentan reduced UACR from baseline by 28 ± 4%, 62 ± 8% and 63 ± 6% at 10, 20 and 30 mg/kg/day, respectively

3. Plasma atrasentan concentrations
   - Few (1) [atrasentan] plasma concentrations covered the ET<sub>2</sub> Ki<sub>1</sub> and were highly selective over ET<sub>1</sub> consistent with human exposures (0.75 mg/dL)

Table 1. Atrasentan plasma concentrations at baseline and following treatment with varying doses of atrasentan in gddY mice:

<table>
<thead>
<tr>
<th>Dose (mg/kg/day)</th>
<th>Baseline (nmol/L)</th>
<th>Day 3 (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>7.8</td>
<td>7.6</td>
</tr>
<tr>
<td>20</td>
<td>39</td>
<td>2.9</td>
</tr>
<tr>
<td>30</td>
<td>99</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>0.0133</td>
<td>704</td>
</tr>
</tbody>
</table>

Conclusion

- Atrasentan, a potent and selective ET<sub>2</sub> antagonist, leads to rapid reductions in albuminuria with intra-renal transcriptional downregulation of proinflammatory and fibrotic signaling in the gddY mouse model
- The dynamic transcriptional changes in the kidney, including downregulation of known direct ET<sub>2</sub> receptor target genes, following only 5 days of treatment and prior to sustained long-term reductions in albuminuria and blood pressure that could mediate this benefit, is consistent with direct anti-inflammatory and antifibrotic effects of ET<sub>2</sub> blockade in IgAN
- These results support further characterization of the effects of long-term treatment of atrasentan in the gddY mouse and support the therapeutic potential of atrasentan in IgA to reduce proteinuria and kidney inflammation and fibrosis, key drivers of IgAN progression
- The Phase 3 ALIGN trial is assessing the efficacy, safety and tolerability of atrasentan in IgAN patients at risk of progressive kidney function loss, despite optimized RAS blockade

References

1. Tycova et al., Physiol. Res. 67: 93-105, 2018
4. Heerspink et al., SONAR Trial, 2019