Efficacy of tenapanor to treat hyperphosphatemia in patients on hemodialysis

Geoffrey A Block,1 David P Rosenbaum,2 Paul Korner,2 Andrew Yan,2 Glenn M Chertow3

1Denver Nephrology Research, Denver, CO, USA; 2Ardelyx, Inc., Fremont, CA, USA; 3Stanford University School of Medicine, Stanford, CA, USA

Presented at the American Society of Nephrology Kidney Week 2017, October 31–November 5, New Orleans, LA, USA.

Table 1. Patient demographics and baseline characteristics (safety population)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>3 mg b.i.d.</th>
<th>10 mg b.i.d.</th>
<th>Pooled tenapanor</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>61 ± 14</td>
<td>65 ± 14</td>
<td>64 ± 14</td>
<td>63 ± 13</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>42 (60%)</td>
<td>46 (60%)</td>
<td>44 (62%)</td>
<td>48 (62%)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72 ± 24</td>
<td>75 ± 24</td>
<td>74 ± 23</td>
<td>73 ± 23</td>
</tr>
<tr>
<td>White</td>
<td>30/41</td>
<td>25/34</td>
<td>30/40</td>
<td>31/35</td>
</tr>
<tr>
<td>Black or African American</td>
<td>4/0</td>
<td>6/0</td>
<td>4/0</td>
<td>6/0</td>
</tr>
<tr>
<td>Other</td>
<td>1/7</td>
<td>1/7</td>
<td>1/7</td>
<td>1/7</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>13 (18%)</td>
<td>16 (22%)</td>
<td>14 (19%)</td>
<td>15 (19%)</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>6 (8%)</td>
<td>7 (10%)</td>
<td>6 (8%)</td>
<td>7 (10%)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>14 (19%)</td>
<td>15 (21%)</td>
<td>15 (20%)</td>
<td>15 (20%)</td>
</tr>
<tr>
<td>Plasma creatinine, mg/dL</td>
<td>9.2 ± 3.7</td>
<td>9.4 ± 3.8</td>
<td>9.3 ± 3.8</td>
<td>9.5 ± 4.0</td>
</tr>
<tr>
<td>ESRD duration, years</td>
<td>12 ± 12</td>
<td>13 ± 13</td>
<td>12 ± 13</td>
<td>13 ± 13</td>
</tr>
</tbody>
</table>

Methods

This was a double-blind study with an 8-week randomized treatment period followed by a 4-week randomized placebo-controlled withdrawal period (ClinicalTrials.gov identifier NCT02675998) (Figure 1). The study was conducted with the Declaration of Helsinki at 32 sites in the USA, with all patients providing written informed consent. Adults (18–40 years of age) with chronic kidney disease stage 5D (hemodialysis) who were receiving at least three daily doses of phosphate binder medication were eligible for inclusion.

• Following a 4- to 8-week washout of phosphate binders, patients who had serum phosphate concentrations of 6.0–10.0 mg/dL and an increase of at least 1.5 mg/dL, from screening were randomized (1:1:1) to receive a single tablet of tenapanor 3 mg, 10 mg or 30 mg twice daily (b.i.d.) for 8 weeks.

• In the 30 mg b.i.d. group, weekly stepwise down-titration (30 mg to 15 mg to 3 mg b.i.d.) was permitted during the first 4 weeks based on gastrointestinal tolerability (hereafter referred to as “tenapanor 30 mg b.i.d. titration”).

• At the end of the 8-week randomized treatment period, patients entered a 4-week randomized withdrawal period, in which they were randomized to:
  - remain on their dose of tenapanor (data from all three dose groups during the withdrawal period were hereafter referred to as the “tenapanor group”)
  - remain on their dose of tenapanor (data from all three dose groups during the withdrawal period were hereafter referred to as the “placebo group”)

• The primary efficacy endpoint, based on the responder population, was the difference in least-squares mean (LSM) change from baseline to week 8 in the responder population in the change in serum phosphate concentration from the end of the 8-week treatment period to the end of the 4-week withdrawal period.

• The responder population was defined as patients achieving a decrease in serum phosphate concentration of at least 1.2 mg/dL during the randomized treatment period.

• Other endpoints – intent-to-treat population

• Serum parathyroid hormone concentrations were broadly similar across groups and no significant changes were noted in either of the two treatment periods (Table 2).

• The LSM change in median serum fibroblast growth factor 23 (FGF23) concentrations at baseline (Table 2).

• A significant reduction from baseline to the end of the 8-week treatment period (p < 0.002) was observed in the tenapanor 30 mg b.i.d. titration group.

• At the end of the 4-week randomized withdrawal period, there was no significant difference in median serum FGF23 concentration between the pooled tenapanor and placebo groups.

Conclusions

• In this phase 3 randomized trial of tenapanor treatment in patients with hyperphosphatemia undergoing hemodialysis, there was a statistically significant difference between tenapanor and placebo in the change in serum phosphate concentration over the 4-week randomized withdrawal period in the responder population, which was the primary efficacy endpoint.

• Tenapanor provided statistically significant reductions from baseline in serum phosphate concentration over 8 weeks of treatment in all three dose groups.

• Tenapanor, with its novel mechanism of action involving reduction of serum phosphate concentration, may prove useful in the treatment of hyperphosphatemia.

References

5. Zhou X et al. Accepted Abstract at the American Society of Nephrology 2016 meeting, San Diego, CA, USA, 2016; abstract number V-1241.

Disclosures

This study was sponsored by Ardelyx and all the authors have received or will receive research support from Ardelyx. Paul Korner is a former employee of and has continued to provide consultancy services to Ardelyx. Geoffrey Block serves as a consultant to Ardelyx and has research funding from Ardelyx. His practice has received ownership interest in Ardelyx.

Acknowledgments

The authors would like to thank all patients, investigators, staff, and site sponsors at the 32 sites who participated in this study. Medical writing support was provided by Eleanor Heads (PHS) from Pharmaceutical Solutions, London, UK, and was funded by Ardelyx.

Table 2. Changes in serum phosphate concentration in the intent-to-treat population

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline phosphate (mg/dL)</th>
<th>Change from end of 8-week randomized treatment period to end of 4-week randomized withdrawal period (LSM (95% CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenapanor 3 mg b.i.d</td>
<td>4.30 ± 1.38</td>
<td>−1.06 (−1.72, −0.40)</td>
</tr>
<tr>
<td>Tenapanor 10 mg b.i.d</td>
<td>4.90 ± 1.50</td>
<td>−0.57 (−1.22, 0.08)</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.10 ± 1.48</td>
<td>0.60 (−0.25, 1.45)</td>
</tr>
</tbody>
</table>

Figure 1. Study design.

Figure 2. Change in serum phosphate concentration in the responder population at the end of the 8-week randomized treatment period (a) and from the end of the 8-week randomized treatment period to the end of the 4-week randomized withdrawal period (b).

Figure 3. Change in serum phosphate concentration in the intent-to-treat population at the end of the 8-week randomized treatment period (a) and from the end of the 8-week randomized treatment period to the end of the 4-week randomized withdrawal period (b).

Figure 3a.

Figure 3b.

Figure 4.

Figure 5.

Figure 6.