Indirect Comparison Of Patisiran and Tafamidis For Treatment Of Hereditary Transthyretin-Mediated (hATTR) Amyloidosis With Polyneuropathy

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Background and Rationale

Hereditary Transthyretin-Mediated (hATTR) Amyloidosis
- Rare, inherited, rapidly progressive, life-threatening, multi-systemic disease caused by mutations in the transthyretin (TTR) gene resulting in debilitating morbidity and high mortality.
- Cardiomyopathy, polyneuropathy, photoreceptor degeneration.
- Median survival of 4 years, with a range of 2-15 years.

Methods (cont.)

Systematic Literature Review (SLR)
- Identified 18 publications describing one randomized, placebo-controlled clinical trial of tafamidis versus placebo (Fx-005) in patients with hATTR amyloidosis.

Results

Systematic Literature Review (SLR)
- Identified 18 publications describing one randomized, placebo-controlled clinical trial of tafamidis versus placebo (Fx-005) in patients with hATTR amyloidosis.

Safety
- (not compared as part of this analysis)
- All treatments were generally well tolerated, with low rates of discontinuations due to adverse events (AEs) (Table 3).
- In each trial, the frequency of AEs and Serious AEs (SAEs) were similar between treatment and placebo.

Table 3: Key safety outcomes in APOLLO (patisiran) and Fx-005 (tafamidis)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Patisiran (p=0.005)</th>
<th>Fx-005 (p=0.005)</th>
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<tbody>
<tr>
<td>AEs Leading to Discontinuation</td>
<td>1.0 [0.1, 3.0]</td>
<td>1.0 [0.1, 3.0]</td>
</tr>
<tr>
<td>Deaths</td>
<td>1.0 [0.1, 3.0]</td>
<td>1.0 [0.1, 3.0]</td>
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</tbody>
</table>

Limitations
- Indirect comparisons can be biased if differences in patient and disease characteristics between trials are effect modifiers (i.e., the relative treatment effect between arms is influenced by a third variable).

Conclusions
- This indirect comparison suggests a benefit of patisiran versus tafamidis in Stage 1 polyneuropathy for patients with hereditary transthyretin (hATTR) amyloidosis.
- The benefit was observed across all endpoints assessed, across the base-case analysis and all sensitivity analyses, and in many cases the difference was statistically significant.