Results of a phase 1b/2 trial of intravitreal (IVT) sepofarsen (QR-110) antisense oligonucleotide in Leber congenital amaurosis 10 (LCA10) due to p.Cys998X mutation in the CEP290 gene

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High Unmet Medical Need in LCA10

- Autosomal-recessive mutations in the *CEP290* gene
  - Can be detected as at least one of the two CEP290 mutations in >50% of LCA10 patients\(^1\)-\(^3\)
  - *CEP290* c.2991+1655A>G (p.Cys998X) mutation accounts for up to 21% of all LCA cases\(^1\)-\(^3\)

- Lack of functional CEP290 protein leads to disruption of protein interactions, which induces photoreceptor degeneration\(^4\),\(^5\)

- Severe visual impairment manifests in infancy or early childhood\(^1\),\(^6\)
  - 60–90% reporting severe vision impairment\(^4\)
  - Usually from legally blind to light perception or no light perception

- No approved treatments

CEP290, centrosomal protein 290 kDa; LCA10, Leber congenital amaurosis 10; ONL, outer nuclear layer.

Splice correction for c.2991+1655A>G CEP290 mRNA (p.Cys998X)

**Sepofarsen (QR-110) for LCA10**

- A 17-mer 2'-O-methyl modified phosphorothioate antisense RNA oligonucleotide
- **Binds to the target pseudo-exon region and prevents recognition by splice factors**
- Normal CEP290 splicing of the pre-mRNA transcript and production of full-length CEP290 protein
- Sepofarsen (QR-110) induces mRNA editing and cilia growth in c.2991+1655A>G-LCA10 patient-derived retinal organoids

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Enrolled 11 LCA10 patients (age range 8-44) homozygous or compound heterozygous for the c.2991+1655A>G (p.Cys998X) mutation

- Up to 4 intravitreal injections to the study eye, defined as the worse-seeing eye
- 3 participating sites: sites in EU (UGhent) and US (UPenn, UIowa)

**Objectives:**
- Primary outcomes: Safety/tolerability
- Secondary outcomes: best corrected visual acuity (BCVA), full-field stimulation (FST), Identify target dose, Mobility course feasibility in LCA10
Baseline Demographics and Genotypes

<table>
<thead>
<tr>
<th></th>
<th>Sex</th>
<th>2nd CEP290 Allele</th>
<th>Age/Group</th>
<th>Baseline VA</th>
<th>Treated</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(M/F)</td>
<td>(Adult/Ped)</td>
<td>[log MAR]</td>
<td>Eye</td>
<td>[µg]</td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td>M</td>
<td>c.2506_2507delGA</td>
<td>19 / A</td>
<td>LP / LP</td>
<td>RE</td>
<td>160/80</td>
</tr>
<tr>
<td>P2</td>
<td>M</td>
<td>c.4723A&gt;T</td>
<td>41 / A</td>
<td>LP / LP</td>
<td>RE</td>
<td>160/80</td>
</tr>
<tr>
<td>P3</td>
<td>M</td>
<td>c.5668G&gt;T</td>
<td>44 / A</td>
<td>2.4 / 2.3</td>
<td>LE</td>
<td>160/80</td>
</tr>
<tr>
<td>P4</td>
<td>F</td>
<td>c.4438-3delC</td>
<td>16 / P</td>
<td>2.5 / 2.5</td>
<td>RE</td>
<td>160/80</td>
</tr>
<tr>
<td>P5</td>
<td>M</td>
<td>c.6277delG</td>
<td>8 / P</td>
<td>1.9 / 2.1</td>
<td>LE</td>
<td>160/80</td>
</tr>
<tr>
<td>P6</td>
<td>F</td>
<td>c.3167_3168insA</td>
<td>21 / A</td>
<td>LP / LP</td>
<td>RE</td>
<td>320/160</td>
</tr>
<tr>
<td>P7</td>
<td>F</td>
<td>c.4723A&gt;T</td>
<td>27 / A</td>
<td>1.1 / 0.7</td>
<td>RE</td>
<td>320/160</td>
</tr>
<tr>
<td>P8</td>
<td>M</td>
<td>c.6277delG</td>
<td>10 / P</td>
<td>1.9 / 1.4</td>
<td>RE</td>
<td>320/160</td>
</tr>
<tr>
<td>P9</td>
<td>F</td>
<td>c.4393C&gt;T</td>
<td>24 / A</td>
<td>LP / LP</td>
<td>RE</td>
<td>320/160</td>
</tr>
<tr>
<td>P10</td>
<td>F</td>
<td>c.547_550delTACC</td>
<td>15 / P</td>
<td>LP / LP</td>
<td>RE</td>
<td>320/160</td>
</tr>
<tr>
<td>P11</td>
<td>F</td>
<td>c.2991+1655A&gt;G</td>
<td>14 / P</td>
<td>0.6/0.6</td>
<td>LE</td>
<td>160/80</td>
</tr>
</tbody>
</table>

AAO2020 Online - Results sepolfarsen clinical study
## Results - Safety Summary

<table>
<thead>
<tr>
<th>SAE/AE</th>
<th>Cataracts</th>
<th>Cystoid Macular Edema</th>
<th>Retinal thinning</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 SAE (surgery)/2 AE</td>
<td>0 SAE / 2 AE</td>
<td>0 SAE / 2 AE</td>
</tr>
<tr>
<td>Timing (160μg/80μg cohort)</td>
<td>8-12 months</td>
<td>No cases</td>
<td>No cases</td>
</tr>
<tr>
<td>Timing (320μg/160μg cohort)</td>
<td>3-9 months</td>
<td>3-4 months</td>
<td>3-10 months</td>
</tr>
<tr>
<td>Treatment-responsive</td>
<td>Yes</td>
<td>Yes</td>
<td>Stabilized</td>
</tr>
</tbody>
</table>
**Results – Mean Efficacy**

**All Treated Subjects (n=11)**

Visual acuity peak associated with cataract occurrence. These subjects regained their pre- cataract visual acuity after surgery.

<table>
<thead>
<tr>
<th>Eye</th>
<th>BCVA – LogMAR (n=11)</th>
<th>Red FST – log cd/m² (n=10)</th>
<th>Blue FST – log cd/m² (n=10)</th>
<th>Mobility course – composite score (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated (TE)</td>
<td>-0.55 (0.26) p&lt;0.05 vs. CE</td>
<td>-0.91 (0.18) p&lt;0.01 vs. CE</td>
<td>-0.79 (0.23) p&lt;0.02 vs. CE</td>
<td>2.5 (0.99) p=0.1 vs. CE</td>
</tr>
<tr>
<td>Untreated (CE)</td>
<td>-0.12 (0.07)</td>
<td>-0.16 (0.16)</td>
<td>0.02 (0.11)</td>
<td>1.75 (0.75)</td>
</tr>
</tbody>
</table>

*Visual acuity peak associated with cataract occurrence. These subjects regained their pre- cataract visual acuity after surgery.
Conclusions – Sepofarsen for LCA10

• 12-month results from Phase 1/2 safety and dose-ranging trial

• The RNA antisense oligonucleotide sepofarsen had a manageable safety profile in adults and children with LCA10 specifically in 160µ/80µg dose cohort
  • Cataracts are primary adverse event (AE; N=8)
    • Onset earlier in 320µg/160µg compared to 160µg/80µg cohort
    • Standard cataract surgery performed in 6 subjects with restoration of pre-cataract vision
  • Cystoid macular edema and retinal thinning not observed in 160µg/80µg dose cohort
  • No systemic AEs, those related to injections self-limited

• First treatment to show statistically significant differences for the within-subject improvement in mean visual acuity, and FST, supporting the strength of a potential therapeutic benefit

• Subjects: Extension trial ongoing and Phase 2b/3 trial recruiting (Illuminate; NCT03913143).
References