A Natural History Study of Subjects with X-linked Retinoschisis in Anticipation of a Phase I/II Gene Therapy Trial

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X-linked Retinoschisis Background

- Rare X-Linked recessive
- Incidence: 1:5,000 to 1:30,000
- Prevalence: ~35,000 patients in US and EU
- Mutations in single gene RS1 in all cases

Retinoschisin
- 24 kDa protein secreted by photoreceptor and bipolar cells
- Forms extracellular homo-octameric complexes around photoreceptor inner segments, OPL and INL
- Maintains retinal cellular organization and synaptic structure
Clinical Features of X-Linked Retinoschisis

Clinical Features
- Family History
- Decreased central vision
- Maculoschisis (100%)
- Peripheral schisis (50%)
- Vitreous Hemorrhage
- Retinal Detachments
- Negative waveform ERG

Images: Santos et al. 2005 and CEI
Additional Testing Modalities in XLRS

Kinetic Visual Fields

Static Visual Fields

Multifocal ERG

Microperimetry
This is an exciting time for Patients with X-Linked Retinoschisis

**Two Gene Therapy Trials:**

**NCT02317887** - NIH
Study of RS1 Ocular Gene Transfer for X-linked Retinoschisis

**NCT02416622** - AGTC
Safety and Efficacy of rAAV-hRS1 in Patients With X-linked Retinoschisis (XLRS)
Critical Questions

How progressive is this disease?

What might be good endpoints for a trial?

Do carbonic anhydrase inhibitors make a difference?
Natural History Study in XLRS

- **Inclusion:** Males, Confirmed mutation in RS1, Age ≥ 6 yrs.
- **Study Design:** 3 year, Phase 0 longitudinal study
- **Enrollment:** 55 patients
- **Sites:**
  - Casey Eye Institute (OHSU)
  - Kellogg Eye Center (U. Mich.)
  - Retina Foundation of the Southwest
- **Primary Endpoints:**
  - Change in time of: BCVA, Visual Fields, SD-OCT, ERG
- **Secondary Endpoints:**
  - Response to Carbonic Anhydrase Inhibitors
### Spectrum of Mutations in Natural History Study

<table>
<thead>
<tr>
<th>Subject#</th>
<th>Mutation</th>
<th>Mutation Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFS-304</td>
<td>c.1A&gt;T p.M1L</td>
<td>Missense mutation</td>
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<tr>
<td>RFS-316</td>
<td>c.1A&gt;T p.M1L</td>
<td>Missense mutation</td>
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<td>KEC-006</td>
<td>c.35T&gt;A; c.52+5G&gt;C p.L12H</td>
<td>Missense/Splice site</td>
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<td>CEI-022</td>
<td>c.96dupC;p.Trp33Leufs*53</td>
<td>Duplication</td>
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<td>CEI-002</td>
<td>c.99G&gt;A p.W33Stop</td>
<td>Missense mutation</td>
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<tr>
<td>CEI-005</td>
<td>c.99G&gt;A p.W33Stop</td>
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<td>CEI-020</td>
<td>c.203C&gt;G p.R68R</td>
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<td>KEC-004</td>
<td>c.208G&gt;A p.G70S</td>
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<td>c.214G&gt;A p.E72K</td>
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<td>c.223dup</td>
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<td>c.288T&gt;C p.W96R</td>
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<td>c.304C&gt;T p.R102W</td>
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<td>RFS-313</td>
<td>c.520delC</td>
<td>Deletion</td>
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<td>c.574C&gt;T p.P192S</td>
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<td>Exon 1 deletion</td>
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<td>CEI-021</td>
<td>Exon 2 deletion</td>
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</table>

### Mutations by Class

- **Deletion**
- **Splicing**
- **Duplication**
- **Nonsense**
- **Missense**
• Weak correlation of decreased visual acuity with age
• Need greater than 2 line change for significance
Larger targets useful for safety, but probably not as useful for efficacy
Cross-sectional Baseline Hill of Vision Volume vs. Age

Octopus 900 Static Perimetry

Hill of Vision (Static Perimetry, V4e Target)

R² = 0.2484

Hill of Vision (Static Perimetry, III4e Target)

R² = 0.1786

VFMA – Hill of Vision Volume
**Problem:** Total Retinal thickness is a combination of schisis and atrophy
Automatic Segmentation

ILM

Cysts

RPE

After Manual Correction

Developed by Tomy Tan, PhD, David Huang MD/PhD
Cyst Thickness Map

Cyst Volume = 0.864 mm$^3$
Spectrum of Baseline Cyst Volume
How Does Treatment with Carbonic Anhydrase Inhibitors influence XLRS?
CAI subgroup – Cyst Volume Change over time

Right Eye

BCVA=52

Volume 0.170 mm³

BCVA=56

Volume 0.158 mm³

BCVA=55

Volume 0.026 mm³

BCVA=56

Volume 0.008 mm³

Left Eye

BCVA=57

Volume 0.946 mm³

BCVA=59

Volume 0.930 mm³

BCVA=56

Volume 0.090 mm³

BCVA=58

Volume 0.070 mm³
CAI subgroup – Cyst Volume Change over time

Right Eye

BCVA=69

BCVA=73

BCVA=73

BCVA=76

0.884 mm³

0.895 mm³

0.573 mm³

0.841 mm³

Left Eye

BCVA=56

BCVA=50

BCVA=54

BCVA=60

0.749 mm³

0.742 mm³

0.638 mm³

0.908 mm³

Screening

1 month

3 month

6 month
Natural History Study Conclusions

• Cross-sectional and natural history of XLRS demonstrates slow progression

• To demonstrate efficacy of a clinical trial improvement of structure of function will be needed

• Treatment with CAIs in XLRS
  • Minimal effect on cyst volume and visual acuity
  • Occasional patient has a good response
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