OIS @ AAO

Barrett Katz, MD, MBA
Chief Medical Officer

GS010 - REVERSE Phase III Trial @ 72 Weeks
GS030 - Development Update

Chicago, October 25, 2018
GS010
REVERSE Phase III Week 72 Results
Leber Hereditary Optic Neuropathy (LHON)
Leber’s Hereditary Optic Neuropathy

IS NOT

Leber’s Congenital Amaurosis
Leber’s Hereditary Optic Neuropathy

An genetically determined form of blindness

Most-common inherited mitochondrial disease

Rapid sequential loss of VA in young adults

11778-ND4 genotype = ~ 75% of LHON in NA/EU
GenSight’s proprietary Mitochondrial Targeting Sequence (MTS) technology

The only technology that permits missing mitochondrial proteins to be actively shuttled into the mitochondrial to restore energy production.

Replacement Gene: rAAV2/2-ND4 (GS010)

Transfection of RGC

Transcribed into mRNA

Protein synthesized & Translocated into mitochondrion
GS010: From Bench to Bedside

**In vitro**
- GS010 restores respiratory chain complex I in patients fibroblasts

**In vivo**
- GS010 prevents optic atrophy and visual loss in LHON rats

**First in man**
- GS010 Phase I trial demonstrates safety and tolerability, as well as trends of efficacy

<table>
<thead>
<tr>
<th>Study Phase</th>
<th>Study Name</th>
<th>Recruitment</th>
<th>Data Readout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I/Iia</td>
<td>CLIN01</td>
<td>✔ Complete</td>
<td>✔ 2.5 years reported</td>
</tr>
<tr>
<td>Phase III</td>
<td>RESCUE 0-6 months</td>
<td>✔ Complete</td>
<td>☐ 48W Topline expected early Q1 2019</td>
</tr>
<tr>
<td>Phase III</td>
<td>REVERSE 6-12 months</td>
<td>✔ Complete</td>
<td>✔ 48W Topline reported in April 2018&lt;br&gt;✔ 72W results reported on Oct.18, 2018</td>
</tr>
<tr>
<td>Phase III</td>
<td>REFLECT Bilateral</td>
<td>☐ Ongoing</td>
<td>☐ Topline expected H1 2020</td>
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<tr>
<td>Phase III</td>
<td>RESCUE-REVERSE Long-Term Follow Up</td>
<td>☐ Ongoing</td>
<td>☐ Expected H2 2019</td>
</tr>
<tr>
<td>LHON REGISTRY</td>
<td>REALITY</td>
<td>☐ Ongoing</td>
<td>☐ Expected 2020</td>
</tr>
</tbody>
</table>
Phase III Clinical TRIALS = RESCUE & REVERSE

Single IVT one eye; fellow eye SHAM control

NCT02652767
RESCUE
Vision loss duration of 6 months or less

NCT02652780
REVERSE
Vision loss duration of >6 months up to 1 year

Week 72 results available

• Confirmed **G11778A** mutation
• Baseline vision $\geq$ Count Fingers
REVERSE Efficacy Analysis

Visual Function

High-Contrast Visual Acuity chart (ETDRS)

Low-Contrast Visual Acuity chart (Pelli-Robson)

Anatomical Biomarkers on OCT

Retinal layers:
- RNFL = axons of RGCs
- GCL = cell bodies of RGCs
HCVA [ETDRS] CHANGE FROM BASELINE TO WEEK 72

Change from Baseline in Letters Read

- Baseline
- Week 12
- Week 24
- Week 48
- Week 72

Study Week

Change in Letters with 95% CI

- GS010
- Sham

+11
+10
+12
+15
REVERSE Week 72 – EFFICACY: Continuous Improvement of CS

Mean change from baseline in LogCS

Weeks after administration

GS010 (N=37)  SHAM (N=37)

-0.05  0  0.05  0.1  0.15  0.2  0.25
0  10  20  30  40  50  60  70  80

GENSIGHT

OCT 2018 – Non Confidential
## REVERSE Results at Week 72 – EFFICACY: Contrast Sensitivity Responders

### Contrast Sensitivity: Responders at Week 72

<table>
<thead>
<tr>
<th>Improvement by 0.3 LogCS</th>
<th>GS010 Eyes n (%)</th>
<th>Sham Eyes n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder Rate</td>
<td>17 (45.9%)</td>
<td>9 (24.3%)</td>
<td></td>
</tr>
<tr>
<td>Non Responder Rate</td>
<td>20 (54.1%)</td>
<td>28 (75.7%)</td>
<td></td>
</tr>
</tbody>
</table>

**McNemar Statistic**

0.0047
### Change of GCL Macular Volume from Baseline to Week 72

<table>
<thead>
<tr>
<th>GCL Macular Volume (mm$^3$)</th>
<th>n</th>
<th>LS Mean (SE)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated Eyes</td>
<td>34</td>
<td>0.000 (0.012)</td>
<td></td>
</tr>
<tr>
<td>Sham Eyes</td>
<td>34</td>
<td>-0.044 (0.012)</td>
<td></td>
</tr>
<tr>
<td>Difference between Treated Eyes and Sham Eyes</td>
<td>34</td>
<td>0.044</td>
<td>0.0060</td>
</tr>
</tbody>
</table>

First demonstration of neuroprotection of CNS NEURONS in a human genetic disease
## REVERSE Week 72 – EFFICACY: ETDRS Macular Volume Significantly Preserved

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</thead>
<tbody>
<tr>
<td><strong>ETDRS Total Macular Volume (mm³)</strong></td>
<td><strong>n</strong></td>
<td><strong>LS Mean (SE)</strong></td>
<td><strong>p-value</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Treated Eyes</strong></td>
<td>34</td>
<td>-0.159 (0.046)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sham Eyes</strong></td>
<td>34</td>
<td>-0.261 (0.046)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Difference between Drug and Sham Eyes</strong></td>
<td>34</td>
<td><strong>0.102</strong></td>
<td><strong>0.0077</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Wilcoxon Signed-Rank Test</strong></td>
<td></td>
<td></td>
<td><strong>0.0042</strong></td>
<td></td>
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</tbody>
</table>
Favorable safety profile of rAAV2/2-ND4 (GS010):

• Most-common adverse events:
  - Ocular Inflammation: anterior and intermediate uveitis
    o 89.2% (33/37) GS010 eyes
    o 8.1% (3/37) SHAM eyes
  - Punctate keratitis:
    o 29.7% (11/37) GS010 eyes
    o 32.4% (12/37) SHAM eyes
  - IOP elevation:
    o 27.0% (10/37) GS010 eyes
    o 2.7% (1/37) SHAM eyes

• Only 1 Serious Adverse Event (systemic: myocardial infarction)

• No adverse events led to study discontinuation
1. Primary efficacy endpoint = Drug treated eyes gained +15 letters, sham treated eyes gained +11

2. Statistically significant protection of RGC GS010 vs. sham (p=0.0060)

3. Statistically significant protection P-M bundle GS010 vs. sham (p=0.0362)

4. CS Responder rate showed improvement of 0.3 LogCS in 45.9% in drug treated eyes vs. 23.3% for sham eyes (p= 0.0047)

5. GS010 with good safety profile
When Primary Efficacy Endpoint is not reached ...

Trials viewed as BINARY events

• *Overly simplistic*

• *Was the PEE appropriate?*

• Generalized estimating equation (GEE) model used to assess if treatment reached VA of $\geq 20/200$ acuity: *GS010-treated eyes significantly more likely to achieve 20/200 or better HCVA than sham-treated eye* ($p=0.0012$)

• *20/200 or worse is where pts wind up on their own*
GenSight: *is our cup half full or half empty?*
GS010: An Accelerated Path to Market

Objective: European marketing authorization submission for GS010 in Q4 2019
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