Suprachoroidal Administration of Small Molecule and Nanoparticle Suspensions: Pre-Clinical Results Correlate to Clinical Trial Outcomes

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• TC: Clearside Biomedical - Employee & Shareholder
• VK: Clearside Biomedical - Employee & Shareholder
Injection into the Suprachoroidal Space (SCS)

Suprachoroidal Injection (SCI) with the SCS Microinjector®
Durability in the SCS for particles ranging from the size of small molecule suspensions, to DNA nanoparticles, to AAV

**Chorioretinal Selectivity of SCS Administration**

*SCS Administration of various particle sizes in rabbit model*

**Fundus Images under Fluorescence in vivo, 60 days post injection**

- **1 µm particles**
- **10 µm particles**

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Preclinical efficacy corroborated in PEACHTREE Ph 3 trial for small molecule triamcinolone acetonide (TA)

**Preclinical**

![Graph showing mean Hacket/McDonald ocular scores over time for different treatment groups.]

**Clinical Trial**

**PEACHTREE Met its Primary Endpoint: Efficacy Data**

Subjects gaining ≥15 BCVA letters from baseline, %

- CLS-TA (N=96): 46.9%
- Control (N=64): 15.6%

Source: Gilger, et al, Treatment of Acute Posterior Uveitis in a Porcine Model by Injection of Triamcinolone Acetonide into the Suprachoroidal Space Using Microneedles, Physiology and Pharmacology
Preclinical safety & compartmentalization corroborated in PEACHTREE Ph 3 trial for small molecule TA

Values are area under the curve ratios (SCS / IVT) over 91 days in rabbit eyes

- Drug not detected in the aqueous from SCS injection
- 12x Sclera/Choroid/Outer Retina
- 1x Neural Retina
- 0.002x Lens
- 0.03x Iris and Ciliary Body

SCI of TKI (axitinib) and complement inhibitor yielded high and durable drug levels in RPE/choroid/sclera

Drug depot in RPE/choroid/sclera

Rabbit Model

*References for in-vitro IC50 range:
Inlyta, EMA. 2012 May; CHMP assessment report
AMD Vascular Endothelial Growth Factor Treatment Approaches

Current AMD Therapies Predominantly Focus on VEGF-A Blockade, not VEGF Receptors

- Anti-VEGF-A increases VEGF-C\(^1\) & VEGF-D\(^2\)
- Broad VEGF blockade may improve outcomes
- A Phase 2 study yielded better AMD outcomes with anti-VEGF-A,C,D vs anti-VEGF-A

Axitinib Suprachoroidally Injected May Improve Outcomes with Its Broad VEGF Blockade

- Inhibits VEGFR-1, VEGFR-2, VEGFR-3
- Inhibited corneal, retinal, and choroidal angiogenesis in animal models\(^3\)-\(^7\)
- More effective than other TKIs for experimental corneal neovascularization in animal models
- Better ocular cell biocompatibility than other TKIs\(^8\)

Preclinical models demonstrated signs of efficacy with TKI axitinib

In animal models, suprachoroidal axitinib (CLS-AX) treated groups experienced a reduction in severe lesions at Day 21, and significantly reduced vascular leakage.

**% Lesions Grade IV Day 21**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>CLS-AX</th>
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<tbody>
<tr>
<td>88.8%</td>
<td>63.3%</td>
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*Fisher’s Exact p-value = .0002

**NEOVASCIULARIZATION: Leakage**

- **Significantly reduced vascular leakage** (marked region represents original lesion area)
- **Increased vascular leakage** (marked region represents lesion area)
Phase 1/2A Trial Design: OASIS Clinical trial

**Trial Design**
- Open-label study to assess the safety and tolerability of single doses of CLS-AX administered through suprachoroidal injection
- 3 Cohorts of 5 patients each: n=15
- Dose-escalation will begin at 0.03 mg CLS-AX; proceed to next cohort following review by Safety Monitoring Committee

**Cohort Enrollment and Treatment**

<table>
<thead>
<tr>
<th>Screening</th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
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<tbody>
<tr>
<td>2 mg aflibercept dosed at screening (day -28)</td>
<td>CLS-AX dosed at baseline</td>
<td>Aflibercept as needed</td>
<td>Aflibercept as needed</td>
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**Key Inclusion Criteria**
- Active subfoveal choroidal neovascularization secondary to AMD
- Two or more anti-VEGF treatments in the 4 months preceding the screening visit with a meaningful response
- BCVA score of ≥ 20 letters (20/400) and ≤ 75 letters (20/32) with < 5 letters change between screening and baseline to ensure patient stability after anti-VEGF
DNPs offer the potential for safe, efficacious, and repeat dosing ocular gene therapy

Potential Advantages

- **Efficacy**: Demonstrated in numerous ocular animal models
  - Transfer large genes (up to ~20 kb)

- **Safety**: Non-immunogenic, without viral capsid proteins or pre-existing immunity.
  - Potential for repeat dosing
  - Higher doses possible to enhance transfection

Well established literature on DNA nanoparticle gene therapy
Suprachoroidal DNPs demonstrated similar activity to subretinal DNPs

Non Viral-Luciferase, Rabbit CHOROID

Non Viral-Luciferase, Rabbit RETINA

1-way ANOVA, p<0.0001.
Bonferroni’s test: *p<0.05, ** p<0.01, ***p<0.001,
Two Phase 2 Trials Using SCS Microinjector® for delivery of viral vector RX-314

- **RGX-314 for Treatment of wet AMD**
  - Phase 2 AAVIATE trial of suprachoroidal delivery of RGX-314 using SCS Microinjector is ongoing.
  - Initial Safety Data from Cohort 1 expected in early 2021.

- **RGX-314 for Treatment of Diabetic Retinopathy (DR)**
  - Phase 2 ALTITUDE trial of suprachoroidal delivery of RGX-314 using SCS Microinjector is ongoing.
Suprachoroidal delivery of viral-like particle (VLP, AU-011) for choroidal melanoma in Phase 1B/2 Trial

- Suprachoroidal injection of AU-011* resulted in excellent distribution and duration in over 75% of the suprachoroidal space in preclinical models.
- Drug exposure in the SC space lasted for at least 10 days.
- Suprachoroidal injection of AU-011 followed by photoactivation resulted in a robust tumor response in an orthotopic rabbit choroidal melanoma model.

Study results support further evaluation of AU-011 administration directly into the suprachoroidal space as a potential first line treatment for primary choroidal melanoma.

Clinical trial for suprachoroidal delivery of AU-011 ongoing.

* VLP-488 has the same physicochemical characteristics as AU-011. VLP-488 is the same VLP as in AU-011 conjugated to AlexaFluor488.

Suprachoroidal Injection of Small Molecule Suspensions & Nanoparticles

- May provide an office-based method to target pharmacologic agents to the RPE, sclera, choroid, and retina
- Efficacy and safety results in preclinical models corroborated favorable clinical trial results for suprachoroidal delivery of triamcinolone acetonide for ME associated with NIU
- Four clinical trials are currently enrolling that utilize suprachoroidal injection with the SCS Microinjector®
  - Suprachoroidally injected Axitinib for wet AMD
  - Suprachoroidally injected viral vector RX-314 for wet AMD and DR
  - Suprachoroidal injected viral like particle AU-011 for choroidal melanoma

Minimize exposure to non-diseased tissues
Deliver pharmacologic agents to the RPE, sclera, choroid, retina
Thank you