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

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• JM: Clearside Biomedical - Clinical Trial Investigator, Grants
• TC: Clearside Biomedical - Employee & Shareholder
• VK: Clearside Biomedical - Employee & Shareholder
In-office access to posterior ocular tissues via the Suprachoroidal Space (SCS)
To understand the potential of the SCS

1. How do therapies compartmentalize?

2. What drives durability?

3. How do therapies reach the macula?
1. How do therapies compartmentalize?
Suprachoroidal injection of dye shows posterior circumferential spread around the globe in porcine model.

**Cross-section:** Injectate spreads from scleral spur towards macula.

**Top View:** Injectate immediately spreads from injection site to posterior tissues.

*Spreading fluorescing dye visible in SCS*
Suprachoroidally injected axitinib (CLS-AX) shows compartmentalization and durability in rabbit model.

RCS: RPE / Choroid / Sclera
2. What drives durability?
Preclinical data of multiple small molecules support durability potential in the suprachoroidal space in rabbit models.
3. How do therapies reach the macula?
IOP > Anterior SCS Pressure > Posterior SCS Pressure: Drives uveoscleral outflow
Also a driving force for macular distribution after SCS injection

Table 1. Spontaneous pressure measurements (mm Hg)

<table>
<thead>
<tr>
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<th>Anterior cannula</th>
<th>Posterior cannula</th>
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<tbody>
<tr>
<td>IOP</td>
<td>9.4 ± 0.9 (9)*</td>
<td>9.2 ± 0.9 (10)†</td>
</tr>
<tr>
<td>SCSP</td>
<td>8.4 ± 0.9 (9)*</td>
<td>5.8 ± 0.5 (10)†</td>
</tr>
<tr>
<td>IOP-SCSP</td>
<td>0.9 ± 0.2 (9)§</td>
<td>3.5 ± 0.5 (10)§</td>
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Kozu, K., Emi, J. E., Pederson, and C. B. Tom.
Hydrostatic Pressure of the Suprachoroidal Space.
OCT shows anterior and posterior expansion of the SCS post-injection.

**Anterior Expansion**
*Clinical Trial Subject*

**Posterior Expansion to Optic Nerve Head**
*Rabbit Model*

Sources:
Suprachoroidal injection of small molecule concentrations are similar in both retina and RPE / Choroid / sclera tissues.

4. How do these concepts translate to clinical trials?
Preclinical bioavailability corroborated in efficacy of PEACHTREE Ph 3 trial for small molecule triamcinolone acetonide (TA)

Preclinical

High TA levels in the Retina, Sclera/Choroid/RPE of rabbits post suprachoroidal administration of CLS-TA

Clinical Trial

PEACHTREE Met its Primary Endpoint:
Subjects gaining ≥15 BCVA letters from baseline, %

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

Low levels of suprachoroidal administered TA in the anterior spaces compared to intravitreal injection

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

Drug not detected in the aqueous from SCS injection

0.002x SCS/IVT
Lens

0.03x SCS/IVT
Iris and Ciliary Body

12x SCS/IVT
Sclera/Choroid/Outer Retina

1x SCS/IVT
Neural Retina

Preclinical

Clinical Trial

PEACHTREE IOP AE Rates: Safety Data

Rescued Control Patients

All 160 Patients

Percent Subjects

0%
10%
20%
30%

CLS-TA (N=96)

N=11

11.5%

Control (N=64)

N=10

15.6%

N=10/37

IVT or periocular steroid rescue

Suprachoroidal TKI (CLS-AX) now in Phase 1/2 Clinical Trial

Clinical trial currently enrolling

Dose-escalating, open label study to assess the safety and tolerability of CLS-AX in treatment experienced wAMD patients
Suprachoroidal Injection of Small Molecule Suspensions

- Suprachoroidal delivery of small molecule suspensions demonstrate:
  - prolonged therapeutic levels with potential for sustained release
  - compartmentalization to posterior ocular tissues
  - high bioavailability

- Currently, 5 clinical trials evaluating 4 therapies:
  - CLS-AX for wAMD
  - RGX-314 for wAMD
  - RGX-314 for DR
  - AU-011 for Choroidal Melanoma
  - CLS-TA/ARVN001 for DME (China)