Suprachoroidal Delivery of Small Molecule Suspensions and Nanoparticles

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Financial Disclosures

• JK: Advisory Boards – Adverum, Allergan, Clearside Biomedical, Genentech, Notal Vision, Novartis, Regeneron
  Data Safety Monitoring Boards – Gemini, Lineage
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Suprachoroidal Injection of Small Molecule Suspensions and 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
- In preclinical models:
  - Tyrosine kinase inhibitor (TKI, axitinib) and complement inhibitor show promising results
  - Suprachoroidal and subretinal injection of DNA nanoparticles showed similar expression of a marker gene

Minimize exposure to non-diseased tissues

Deliver pharmacologic agents to the RPE, sclera, choroid, retina
Injection into the Suprachoroidal Space (SCS)
Durability in the SCS for particles ranging from the size of small molecules suspensions, to DNA nanoparticles, to AAV

Chorioretinal Selectivity of SCS Administration

SCS Administration of various particle sizes in rabbit model

PEACHTREE: Phase 3, Randomized, Controlled, Double-Masked, Multicenter Trial

Primary Endpoint: Visual Acuity

Suprachoroidal CLS-TA

N=96

Day 0  Wk 4  Wk 8  Wk 12  Wk 16  Wk 20  Wk 24

Active Arm: Suprachoroidal injection of 4 mg CLS-TA

Control Arm: Sham injection procedure

N=64

Day 0  Wk 4  Wk 8  Wk 12  Wk 16  Wk 20  Wk 24

Sham  Sham

Evaluation period – 6 months

Both Arms: Rescue therapy at any time according to pre-specified criteria
Preclinical efficacy corroborated in PEACTTHREE Ph 3 trial for small molecule triamcinolone acetonide (TA)

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 PEACTHREE 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
- 0.002x Lens
- 0.03x Iris and Ciliary Body
- 12x Sclera/Choroid/Outer Retina
- 1x Neural Retina

PEACHTREE IOP AE Rates: Safety Data

All 160 Patients

<table>
<thead>
<tr>
<th></th>
<th>CLS-TA (N=96)</th>
<th>Control (N=64)</th>
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<tr>
<td>Rescued Control Patients</td>
<td>11.5% (N=11)</td>
<td>15.6% (N=10)</td>
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MAGNOLIA: Prospective, Non-interventional, Masked, Observational 24-week Extension Trial

To be eligible for MAGNOLIA, subjects must have completed PEACHTREE and NOT have received rescue medication.

Primary Endpoint: Time to rescue therapy relative to Day 0 of PEACHTREE

Suprachoroidal CLS-TA
N=96
Day 0 → Week 4 → Week 8 → Week 12 → Week 16 → Week 20 → Week 24 → Week 30 → Week 36 → Week 42 → Week 48

Suprachoroidal CLS-TA
N=28

PEACHTREE
N=64
Day 0 → Week 4 → Week 8 → Week 12 → Week 16 → Week 20 → Week 24

MAGNOLIA

Sham

Rescue criteria:
- Loss of 10 letters from either of prior 2 visits
- CST > 320 μm
- ↑ CST of 100 μm or 20% (whichever is lower) from either of prior 2 visits
- Investigator discretion
Preclinical durability corroborated in PEACTHREE & MAGNOLIA trials for small TA

Preclinical

Clinical Trial

Sources: 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 | Phase 3 PEACTHREE data; MAGNOLIA data
SCI of TKI (axitinib) and complement inhibitor yielded high and durable drug levels in RPE/choroid/sclera

Drug depot in RPE/choroid/sclera

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

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 as Day 21, and significantly reduced vascular leakage.

% Lesions Grade IV
Day 21

- Control: 88.8%
- CLS-AX: 63.3%

\*Fisher’s Exact p-value = 0.0002

**NEOVASCULARIZATION: Leakage**

- CLS-AX treated eye: Significantly reduced vascular leakage (marked region represents original lesion area)
- BSS treated eye: Increased vascular leakage (marked region represents lesion area)
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

1-way ANOVA, p<0.0001.
Bonferroni’s test: *p<0.05, ** p<0.01, ***p<0.001,
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