Suprachoroidal Delivery of CLS-TA for Uveitic Macular Edema: Results of the Phase 3 PEACHTREE Trial

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Suprachoroidal Injection for Posterior Segment Disease

Animal model data for suprachoroidal vs. intravitreal injection of TA show:

- Higher amounts of drug in the choroid, RPE cells, and retina
- Lower exposure to the anterior segment

A potentially useful ocular distribution of drug for the treatment of uveitic macular edema
PEACHTREE: Phase 3, Randomized, Controlled, Double-Masked, Multicenter Trial

Visual acuity primary endpoint

Enrollment

N=96

Suprachoroidal CLS-TA

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

Sham

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

Evaluation period – 6 months

Both Arms: Rescue therapy at any time according to pre-specified criteria

Sham
Key Inclusion and Exclusion Criteria

Inclusion

- **Diagnosis of macular edema** with central subfield thickness ≥300 microns
- Noninfectious uveitis of any associated diagnosis/etiology
- Visual acuity: 20/800 to 20/40 (≥5 to ≤70 ETDRS letters)

Exclusion

- Any active ocular disease or infection in the study eye other than uveitis
- Intraocular pressure >22 mmHg or uncontrolled glaucoma
- More than 2 IOP-lowering medications

Subjects could have active or controlled disease at enrollment

ETDRS: Early Treatment Diabetic Retinopathy Study
IOP: intraocular pressure
Baseline Subject Characteristics Were Similar Between Treatment Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CLS-TA n=96</th>
<th>Control n=64</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>42 (43.8)</td>
<td>30 (46.9)</td>
</tr>
<tr>
<td>Female</td>
<td>54 (56.3)</td>
<td>34 (53.1)</td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>50.4 (14.2)</td>
<td>50.0 (15.1)</td>
</tr>
<tr>
<td>BCVA, study eye (ETDRS letters)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>54.7 (13.9)</td>
<td>53.5 (12.9)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>57 (9-89)</td>
<td>54 (12-79)</td>
</tr>
<tr>
<td>CST, study eye (μm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>480.9 (153.2)</td>
<td>525.4 (158.1)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>453 (256-857)</td>
<td>518 (274-971)</td>
</tr>
</tbody>
</table>

CST: central subfield thickness; ETDRS: Early Treatment Diabetic Retinopathy Study
All Anatomic Subtypes Were Enrolled

CLS-TA (N=96)
- Panuveitis: 29.2%
- Posterior: 22.9%
- Intermediate: 35.4%
- Anterior: 28.1%

Control (N=64)
- Panuveitis: 37.5%
- Posterior: 20.3%
- Intermediate: 35.9%
- Anterior: 21.9%
Distribution of Uveitis Diagnosis Was Similar Between Treatment Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CLS-TA (N=96)</th>
<th>Control (N=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>69 (71.9)</td>
<td>44 (68.8)</td>
</tr>
<tr>
<td>Pars planitis</td>
<td>7 (7.3)</td>
<td>4 (6.3)</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>4 (4.2)</td>
<td>5 (7.8)</td>
</tr>
<tr>
<td>HLA-B27 related</td>
<td>4 (4.2)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (3.1)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Juvenile idiopathic arthritis</td>
<td>2 (2.1)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Vogt-Koyanagi-Harada syndrome</td>
<td>1 (1.0)</td>
<td>2 (3.1)</td>
</tr>
<tr>
<td>Reactive arthritis</td>
<td>2 (2.1)</td>
<td>0</td>
</tr>
<tr>
<td>Birdshot retinochoroidopathy</td>
<td>2 (2.1)</td>
<td>0</td>
</tr>
<tr>
<td>Behçet’s syndrome</td>
<td>1 (1.0)</td>
<td>0</td>
</tr>
</tbody>
</table>
PEACHTREE Met Its Primary Efficacy Endpoint

Subjects gaining ≥15 ETDRS letters from baseline, %

Intention-to-treat population; LOCF imputation. The p-value is based on a Cochran-Mantel-Haenszel test for general association between treatment and response with stratification by country.

ETDRS, Early treatment diabetic retinopathy study; LOCF, last observation carried forward.
Mean Change in BCVA

Improvement From as Early as Week 4 Through Week 24 in the CLS-TA Arm

Mean change at week 24 from baseline in BCVA in ETDRS letters read

<table>
<thead>
<tr>
<th>Observation (week)</th>
<th>CLS-TA (N=96)</th>
<th>Control (N=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change, ETDRS letters</td>
<td>13.8</td>
<td>3.0</td>
</tr>
</tbody>
</table>

*p*<0.001 for comparison

Mean change at each visit from baseline in BCVA in ETDRS letters read

<table>
<thead>
<tr>
<th>Observation (week)</th>
<th>CLS-TA</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change, ETDRS letters</td>
<td>9.6</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>11.7</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>11.7</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>12.9</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>12.4</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>13.8</td>
<td>3.0</td>
</tr>
</tbody>
</table>

*Δ*=10.8
*p*<0.001

Intention-to-treat population; last observation carried forward imputation.
t-test. Differences between the CLS-TA and control arms were significant at each visit.
BCVA, best corrected visual acuity.
Mean Change in Central Subfield Thickness

*Improvement From as Early as Week 4 through Week 24 in CLS-TA Arm*

**Mean change from baseline at week 24 in central subfield thickness (µm)**

- **CLS-TA** (N=96) (BSL 481 µm)
- **Control** (N=64) (BSL 525 µm)

- Mean change, CST
  - CLS-TA: -152.6 µm
  - Control: -17.9 µm

**p<0.001 for comparison**

**Mean change at each visit from baseline in central subfield thickness (µm)**

- Observation (week)
- Mean change, CST
  - CLS-TA: -148.5, -145.4, -170.4, -168.0, -152.6 µm
  - Control: -4.2, -25.1, -15.7, -12.7, -10.9, -17.9 µm

**Δ=134.7 µm p<0.001**

Intention-to-treat population; last observation carried forward imputation. BSL, baseline mean value; CST, central subfield retinal thickness.
Resolution of Macular Edema, CST <300 μm
Additional resolution in CLS-TA group at Week 4, Maintained through Week 24

Intention-to-treat population; last observation carried forward imputation.
Less than 300 microns by SD-OCT
CST, central subfield retinal thickness.
Signs of Inflammation
Resolution of Anterior Chamber Cells
*In Subjects With Anterior Chamber Cells at Baseline*

**Percentage of subjects with resolution at week 24**

- CLS-TA (N=50): 72%
- Control (N=23): 17%

*p*<0.001 for comparison

**Percentage of subjects with resolution at each visit from baseline**

- CLS-TA:
  - Week 0: 56%
  - Week 4: 66%
  - Week 8: 62%
  - Week 12: 74%
  - Week 16: 78%
  - Week 20: 72%
  - Week 24:

- Control:
  - Week 0: 22%
  - Week 4: 22%
  - Week 8: 26%
  - Week 12: 30%
  - Week 16: 17%
  - Week 20: 17%
  - Week 24:

Δ=55%

*p*<0.001

Intention-to-treat population: last observation carried forward imputation. The *p*-value is based on a Cochran-Mantel-Haenszel chi-square test for general association stratified by pooled country. Differences between the CLS-TA and control arms were significant at each visit.
Resolution of Anterior Chamber Flare

In Subjects With Anterior Chamber Flare at Baseline

**Percentage of subjects with resolution at week 24**

- **CLS-TA (N=35)**: 74%
- **Control (N=20)**: 20%

*p* < 0.001 for comparison

**Percentage of subjects with resolution at each visit from baseline**

Intention-to-treat population; last observation carried forward imputation. The *p*-value is based on a Cochran-Mantel-Haenszel chi-square test for general association stratified by pooled country. Differences between the CLS-TA and control arms were significant at each visit from week 8.
Resolution of Vitreous Haze

In Subjects With Vitreous Haze at Baseline

**Percentage of subjects with resolution at week 24**

<table>
<thead>
<tr>
<th></th>
<th>Percent subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLS-TA (N=74)</td>
<td>68%</td>
</tr>
<tr>
<td>Control (N=43)</td>
<td>23%</td>
</tr>
</tbody>
</table>

*p<0.001 for comparison*

**Percentage of subjects with resolution at each visit from baseline**

Intention-to-treat population; last observation carried forward imputation. The p-value is based on a Cochran-Mantel-Haenszel chi-square test for general association stratified by pooled country. Differences between the CLS-TA and control arms were significant at each visit.
Kaplan–Meier Analysis: Time to Rescue

- 72% of patients in the control arm required rescue therapy.
- 13% of the patients in the CLS-TA arm required rescue therapy.

Intention-to-treat population
Anatomic location of uveitis
Anatomic location of uveitis

- **Anterior**: Mean change in BCVA = 14.4, p=0.016
- **Intermediate**: Mean change in BCVA = 13.4, p=0.032
- **Posterior**: Mean change in BCVA = 15.6, p=0.005
- **Panuveitis**: Mean change in BCVA = 12.0, p=0.020
Anatomic location of uveitis

![Graph showing mean change in CST (μm) for different anatomic locations of uveitis with p-values for each group: anterior (p=0.229), intermediate (p=0.013), posterior (p=0.021), panuveitis (p=0.002).]
Safety
Safety

Serious AEs
- Three serious AEs, all in CLS-TA arm: none considered treatment-related
  - Two nonocular serious AEs (sialoadenitis, lumbar vertebral fracture)
  - One ocular serious AE (retinal detachment approximately 8 weeks after injection)

<table>
<thead>
<tr>
<th>Ocular AEs in Study Eye</th>
<th>CLS-TA 4.0 mg N=96 n (%)</th>
<th>Control N=64 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects with ≥1 ocular AEs</td>
<td>49 (51.0)</td>
<td>37 (57.8)</td>
</tr>
<tr>
<td>Treatment-related ocular AEs</td>
<td>29 (30.2)</td>
<td>8 (12.5)</td>
</tr>
</tbody>
</table>

Most Frequent AEs
- AEs occurring in >5% subjects in the CLS-TA arm were: elevated IOP (11.5%), eye pain (12.5%), cataract (7.3%)

AEs, adverse events.
Elevated IOP Adverse Events

CLS-TA and Control Subjects

<table>
<thead>
<tr>
<th>Type</th>
<th>CLS-TA</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.5%</td>
<td>10/96</td>
<td>1/84</td>
</tr>
</tbody>
</table>

IOP AE Rates Among Controls by Type of Rescue

<table>
<thead>
<tr>
<th>Type</th>
<th>Percent subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Rescue (n=18)</td>
<td>0%</td>
</tr>
<tr>
<td>Other Rescue (n=8)</td>
<td>0%</td>
</tr>
<tr>
<td>Local Corticosteroid Rescue (n=38)</td>
<td>26.3%</td>
</tr>
</tbody>
</table>

“Elevated IOP” includes (a) increased IOP, (b) ocular hypertension, and (c) glaucoma. AE, adverse event; IOP, intraocular pressure.
Summary of AEs of Elevated IOP*

<table>
<thead>
<tr>
<th>IOP-related Outcome</th>
<th>CLS-TA 4.0 mg</th>
<th></th>
<th>Control</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=96</td>
<td>n (%)</td>
<td>n=64</td>
<td>n (%)</td>
</tr>
<tr>
<td>IOP elevation ≥10 mmHg above baseline at any visit</td>
<td>9 (9.4)</td>
<td></td>
<td>8 (12.5)</td>
<td></td>
</tr>
<tr>
<td>≥30 mmHg at any visit</td>
<td>5 (5.2)</td>
<td></td>
<td>4 (6.3)</td>
<td></td>
</tr>
<tr>
<td>Given IOP lowering meds</td>
<td>10 (10.4)</td>
<td></td>
<td>9 (14.1)</td>
<td></td>
</tr>
<tr>
<td>Any surgical intervention for an elevated IOP AE</td>
<td>0</td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>All AEs of elevated IOP</td>
<td>11 (11.5)</td>
<td></td>
<td>10 (15.6)</td>
<td></td>
</tr>
</tbody>
</table>

*“Elevated IOP” includes the preferred terms (a) IOP increased, (b) ocular hypertension, and (c) glaucoma.
Cataract Adverse Events

- New or worsening cataracts occurred with similar frequency in the CLS-TA and control groups
- No cataract-related surgeries in this trial

“Cataract” includes (a) cataract, (b) subcapsular cataract, and (c) nuclear cataract.
Case example

46 year old AA male with panuveitis OS

Baseline vision: 20/15 OD, 20/40 OS

Baseline IOP: 9 OD, 14 OS

Anterior Segment: 2+ anterior chamber cells, 2+ flare, posterior synechiae from 4-10, Few brown granulomatous KPs inferior OS

Posterior Segment: 1+ vitreous cells, 1+ vitreous haze, Few inferior snowballs, No chorioretinal lesions OS

“Cataract” includes (a) cataract, (b) cataract subcapsular, and (c) cataract nuclear.
Baseline: 20/40 OS, CST 466, IOP 14
Baseline: 20/40 OS, CST 466, IOP 14
3 months: 20/12.5 OS, CST 315, IOP 10
6 months: 20/12.5 OS, CST 303, IOP 12
6 months: 20/12.5 OS, CST 303, IOP 12
PEACHTREE: Take Home Points

**Efficacy**

- PEACTHREE Primary endpoint was met, with ~47% of patients gaining ≥15 ETDRS letters.
- Suprachoroidally injected CLS-TA significantly improved vision and macular edema.
- Visual acuity and macular edema improved irrespective of the anatomic location of uveitis.
- The majority of CLS-TA patients with active inflammation at baseline had resolution of anterior chamber cells, anterior chamber flare and vitreous haze.

**Safety**

Low rates of elevated IOP and cataract
Thank You

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Houston Methodist Hospital