Suprachoroidal CLS-TA Plus Aflibercept Compared with Aflibercept Monotherapy for DME: Analysis of OCT Biomarkers in the Randomized Phase 2 TYBEE Trial

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Disclosures

• Consultant: Boehringer Ingelheim, Thrombogenics, Quark, Omeros, Genentech, Allergan, Novartis, Amgen, Astellas, Alimera

• Research Support: Novartis, Genentech, Clearside, Biogen

• Study Disclosures
  • This study includes research conducted on human subjects. Institutional Review Board approval was obtained prior to study initiation
TYBEE Phase 2 Double-Masked 6-Month DME Trial

(N=36)

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

Primary Endpoint

Randomized (N=71)

Aflibercept PRN Re-Tx Criteria

1. CST ≥ 340 μm
2. ↓BCVA >5 letters & ↑CST >50 μm v. last visit
3. ↓BCVA >9 letters from best measurement & ↑CST >50 μm v. last visit

(N=35)

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

- Sham CLS-TA injections were administered to the aflibercept arm at Day 0 and Wk12.
- Sham aflibercept injections were administered to the combination arm at Wk4 and Wk8

CLS-TA: 4mg triamcinolone acetonide (0.1 mL of 40 mg/mL suspension) delivered into suprachoroidal space.
Aflibercept: 2 mg/0.05 mL
Analysis of Additional Anatomical Outcomes When Comparing Combination Treatment vs. Aflibercept Monotherapy

• *Disorganization of the Retinal Inner Layers (DRIL)*
• Choroidal Vascularity Index (CVI)
Analysis: Disorganization of the Retinal Inner Layers (DRIL)

- Disorganization of the retinal inner layers was defined where 1 or more boundaries between the following layers are not separately identifiable:
  - ganglion cell layer and inner plexiform layer complex
  - inner plexiform layer complex and inner nuclear layer
  - inner nuclear layer and outer plexiform layer
- Performed maximum extent and novel area measurement

DRIL Maximum Extent Illustration

- Manual delineation of DRIL using OCTOR
En Face Projection for DRIL Area
DRIL area map from volume scans

DRIL area = Total retinal area – intact inner retinal area
Similar improvement in maximum extent of DRIL (μm)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Extent Change (μm)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflibercept</td>
<td>-782.2</td>
<td></td>
</tr>
<tr>
<td>Combination</td>
<td>-736.2</td>
<td>0.851</td>
</tr>
</tbody>
</table>

p = 0.851
Similar improvement in area of DRIL (mm$^2$)

Aflibercept: $-3.6$
Combination: $-2.2$

$p=0.349$
Analysis of Additional Anatomical Outcomes When Comparing Combination Treatment vs. Aflibercept Monotherapy

• Disorganization of the Retinal Inner Layers (DRIL)
• Choroidal Vascularity Index (CVI)
Choroidal vascularity index (CVI)

Binarized choroidal luminal area (dark pixels) and stromal area (bright pixels)

CVI = LA/Total Choroidal Area
CVI between study cohorts at baseline and Month 6; change at month 6

<table>
<thead>
<tr>
<th>Study cohorts</th>
<th>CVI (%)</th>
<th>CVI (%) change at M6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Cohort</td>
<td>59.2</td>
<td>1.7</td>
</tr>
<tr>
<td>Control Cohort</td>
<td>60.7</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Change at Month 6

P = 0.95
Multivariate analysis

Summary of Multiple Regression Analysis of the Change from Baseline in Best Corrected Visual Acuity at Week 24 (ITT Population)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline BCVA</td>
<td>0.626</td>
<td>0.1359</td>
<td>(0.353, 0.898)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline CST</td>
<td>-0.053</td>
<td>0.0234</td>
<td>(-0.100, -0.006)</td>
<td>0.028</td>
</tr>
<tr>
<td>Baseline FCSRT</td>
<td>0.049</td>
<td>0.0195</td>
<td>(0.010, 0.088)</td>
<td>0.016</td>
</tr>
<tr>
<td>Baseline Area of DRIL</td>
<td>0.230</td>
<td>0.1847</td>
<td>(-0.142, 0.600)</td>
<td>0.185</td>
</tr>
</tbody>
</table>

BCVA = best corrected visual acuity, CST = central subfield retinal thickness, FCSRT = foveal center subfield retinal thickness, DRIL = disorganization of the retinal inner layer. Analysis performed using regression model using a forward selection technique and a 0.25 significance level for entry into the final model.
Conclusion

• Combination aflibercept & suprachoroidal CLS-TA vs aflibercept monotherapy at Wk24:
  • Similar DRIL improvement (maximum extent)
  • Similar DRIL improvement (area)
  • Similar CVI (no change)

• Of the novel OCT biomarkers we evaluated in this analysis, only area of DRIL was found to be predictive for VA at week 24 (multivariate analysis)
• Area of DRIL is a biomarker that should be considered for evaluation in future DME clinical trials