TANZANITE Phase 2 Retinal vein occlusion (RVO) trial

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RVO treatment hypothesis

The hypothesis to be tested

- **Combination** treatment given **every 3 months** with an **anti-VEGF** and a **corticosteroid** will provide **benefit in visual acuity improvements and reductions in macular edema** that are seen with monthly anti-VEGF alone, and with less frequent treatment (quarterly)
Phase 2 trial – TANZANITE design

This study was a *proof of concept trial* to look for an effect from a suprachoroidally injected drug in RVO patients: in other words, *Can suprachoroidal administration positively affect a retinal vascular disease?*

- Treatment naïve RVO subjects were randomized 1-1
  - **Combination arm:** received *intravitreous aflibercept in addition to suprachoroidal triamcinolone (CLS-TA)*
  - **Aflibercept arm:** received *intravitreous aflibercept alone*

- All subjects were followed for 3 months after treatment at baseline; only additional treatments were intravitreal aflibercept injections
Phase 2 trial in treatment naïve RVO patients

Intravitreous aflibercept + suprachoroidal CLS-TA versus intravitreous aflibercept

**Combination arm:**
Intravitreous aflibercept + suprachoroidal CLS-TA

**Aflibercept arm:**
Intravitreous aflibercept + suprachoroidal sham

(1) Determination for treatments with intravitreous aflibercept at Months 1, 2, and 3 using quantifiable criteria involving the presence of macular edema and decreases in best corrected visual acuity (Loss of 10 letters BCVA, or OCT>340 um)
## Disposition

Patients randomized 46 (23:23)

<table>
<thead>
<tr>
<th>TOTAL NUMBER OF SUBJECTS</th>
<th>Aflibercept arm N=23</th>
<th>Combination arm N=23</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>RANDOMIZED</td>
<td>23</td>
<td>23</td>
<td>46</td>
</tr>
<tr>
<td>COMPLETED</td>
<td>23</td>
<td>23</td>
<td>46</td>
</tr>
<tr>
<td>DISCONTINUED</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SAFETY</td>
<td>23</td>
<td>23</td>
<td>46</td>
</tr>
<tr>
<td>INTENT-TO-TREAT</td>
<td>23</td>
<td>23</td>
<td>46</td>
</tr>
</tbody>
</table>
# Demographics

<table>
<thead>
<tr>
<th></th>
<th>Afiblercept arm N=23</th>
<th>Combination arm N=23</th>
<th>TOTAL N=46</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AGE (YEAR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEAN</td>
<td>65.8</td>
<td>66.9</td>
<td>66.3</td>
</tr>
<tr>
<td>MEDIAN</td>
<td>70.0</td>
<td>67.0</td>
<td>68.0</td>
</tr>
<tr>
<td>MIN, MAX</td>
<td>37, 91</td>
<td>41, 80</td>
<td>37, 91</td>
</tr>
<tr>
<td><strong>SEX n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MALE</td>
<td>10 (43.5)</td>
<td>13 (56.5)</td>
<td>23 (50.0)</td>
</tr>
<tr>
<td>FEMALE</td>
<td>13 (56.5)</td>
<td>10 (43.5)</td>
<td>23 (50.0)</td>
</tr>
<tr>
<td><strong>RACE n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMERICAN INDIAN OR ALASKA NATIVE</td>
<td>1 (4.3)</td>
<td>0</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>BLACK OR AFRICAN AMERICAN</td>
<td>4 (17.4)</td>
<td>3 (13.0)</td>
<td>7 (15.2)</td>
</tr>
<tr>
<td>WHITE</td>
<td>18 (78.3)</td>
<td>20 (87.0)</td>
<td>38 (82.6)</td>
</tr>
</tbody>
</table>
Primary endpoint – number of additional intravitreous aflibercept injections required

There were 14 fewer injections in the Combination arm compared to the Aflibercept arm, or a 61% reduction in the requirement for additional aflibercept.
Number of subjects who received PRN aflibercept

Intent-to-treat (ITT) population: N = 46 (23:23)

Post-hoc analysis

Seventy-eight (78%) percent (18/23) of patients in the combination arm in this trial did not require additional aflibercept treatments during the three-month trial compared to 30% (7/23) in the control, aflibercept arm (p=0.003)
What was learned

• Potential for significantly fewer treatments in a majority of the subjects in the combination arm (aflibercept + CLS-TA) in this study over a three month time-period compared to the subjects who initially received aflibercept only
Change in BCVA

Baseline: 49 ETDRS letters read in each arm

Note: Bars are standard error of the mean; * only month 2 showed p<0.05
## Percent of subjects gaining ≥ 15 letters

<table>
<thead>
<tr>
<th></th>
<th>Aflibercept arm</th>
<th>Combination arm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MONTH 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NUMBER (%) WHO GAINED ≥ 15 LETTERS</strong></td>
<td>09 (39.1)</td>
<td>12 (52.2)</td>
</tr>
<tr>
<td><strong>N=23</strong></td>
<td>N=23</td>
<td></td>
</tr>
<tr>
<td><strong>MONTH 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NUMBER (%) WHO GAINED ≥ 15 LETTERS</strong></td>
<td>09 (39.1)</td>
<td>14 (60.9)</td>
</tr>
<tr>
<td><strong>MONTH 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NUMBER (%) WHO GAINED ≥ 15 LETTERS</strong></td>
<td>10 (43.5)</td>
<td>12 (52.2)</td>
</tr>
</tbody>
</table>
What was learned in terms of functional outcomes

• Potential for **improved visual outcome in the combination arm** compared to the monotherapy aflibercept arm **at Month 1**

• **Improved visual acuity** in the combination arm seen at **Month 1** appears to be **maintained over the 3 months** of the study **with significantly fewer additional injections**.

• These findings were also maintained when CRVO and BRVO patients were examined separately.
Retinal thickness data by SD-OCT (Heidelberg)

- Aflibercept Arm; N=23
- Combination Arm; N=23

Baseline
728 μm and 731 μm in the Aflibercept and Combination arms respectively

Note: Bars are one-sided standard deviations
Percentages of subjects with resolution* of macular edema

*defined as having CST <310 microns on a Heidelberg Spectralis (only OCT in this study required by the protocol)
What was learned for the combination in anatomical outcomes

- Potential for improved anatomical outcome observed in the combination arm compared to the monotherapy arm at Month 1.

- Improved outcome from month 1 was maintained over the 3 months of the study with significantly fewer additional injections.

- These findings were also maintained when CRVO and BRVO patients were examined separately.
## Ocular AEs – details

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Aflibercept arm N=23; n (%)</th>
<th>Combination arm N=23; n (%)</th>
<th>Total N=46; n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataract</td>
<td>0</td>
<td>1 (4.3)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Anterior chamber inflammation</td>
<td>0</td>
<td>1 (20)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>1 (4.3)</td>
<td>2 (8.7)</td>
<td>3 (6.5)</td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td>1 (4.3)</td>
<td>0</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Corneal edema</td>
<td>0</td>
<td>1 (4.3)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Foreign body sensation in eyes</td>
<td>0</td>
<td>1 (4.3)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Eye pain</td>
<td>1 (4.3)</td>
<td>8 (34.8)</td>
<td>19 (19.6)</td>
</tr>
<tr>
<td>Lacrimation increased</td>
<td>0</td>
<td>1 (4.3)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Macular fibrosis</td>
<td>1 (4.3)</td>
<td>0</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Ocular discomfort</td>
<td>2 (8.7)</td>
<td>0</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Ocular hypertension</td>
<td>0</td>
<td>2 (8.7)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Optic disc vascular disorder</td>
<td>1 (4.3)</td>
<td>0</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Optic nerve disorder</td>
<td>0</td>
<td>1 (4.3)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Punctate keratitis</td>
<td>0</td>
<td>1 (4.3)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Retinal degeneration</td>
<td>1 (4.3)</td>
<td>0</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Retinal hemorrhage</td>
<td>0</td>
<td>1 (4.3)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>1 (4.3)</td>
<td>0</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Visual acuity reduced</td>
<td>2 (8.7)</td>
<td>0</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Vitreous detachment</td>
<td>0</td>
<td>1 (4.3)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>0</td>
<td>1 (4.3)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Intraocular pressure increased</td>
<td>0</td>
<td>2 (8.7)</td>
<td>2 (4.3)</td>
</tr>
</tbody>
</table>
Sub-analysis: Perfusion status
### Perfusion status at baseline

**Randomized: 46 (23:23)**

<table>
<thead>
<tr>
<th>PERFUSION TYPE</th>
<th>Aflibercept Arm N=23 (%)</th>
<th>Combination Arm N=23 (%)</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISCHEMIC</td>
<td>5 (21.7)</td>
<td>6 (26.1)</td>
<td>11 (23.9)</td>
</tr>
<tr>
<td>NON-ISCHEMIC</td>
<td>18 (78.3)</td>
<td>17 (73.9)</td>
<td>35 (76.1)</td>
</tr>
</tbody>
</table>
Twenty four percent of subjects in this study were ischemic; they were evenly distributed in the two arms.
Changes from baseline in BCVA for non-ischemic subjects

Slight imbalance in mean BCVA at baseline in non-ischemic subjects with 52 letters read in the combination arm versus 48 letters read in the aflibercept alone arm.

Combination arm: 17 letter gain from baseline at Month 3
Aflibercept arm: 10 letter gain from baseline at Month 3

7 additional letters gained in the combination arm.
Mean CST at baseline in subjects was similar: 708 µm in the combination arm versus 722 µm in the aflibercept alone arm.

Combination arm: 418 µm reduction
Aflibercept arm: 311 µm reduction
Changes from baseline in BCVA for ischemic subjects

There was an imbalance in mean BCVA at baseline in ischemic subjects with **41 letters** read in the **combination arm** versus **49 letters** read in the **aflibercept arm**

- **Combination arm**: 23 letter gain from baseline at Month 3
- **Aflibercept arm**: 16 letter gain from baseline at Month 3
CST changes from baseline for ischemic subjects

There was an imbalance in mean CST at baseline in subjects with CRVO; 796 µm in the combination arm versus 746 µm in the aflibercept alone arm.

- Combination arm: 525 µm reduction
- Aflibercept arm: 455 µm reduction
**Ischemic and non-ischemic take home**

• While the sample size is small, the trends are clear...

• Regardless of perfusion status, combination therapy appears to be better
Phase 3 trial: SAPPHIRE design
Phase 3 RVO program

- **RVO phase 3 trials** are 6 months for efficacy and an additional 6 months follow-up for safety

- **For this combination therapy**
  - Maximal efficacy in the phase 2 study was seen as early as Month 2
  - The phase 3 study was designed to highlight this potential advantage for the combination therapy
SAPPHIRE, Phase 3, trial design

- The SAPPHIRE study incorporates this potential advantage:
  - The primary endpoint of change in BCVA is at Month 2 (the earliest point where maximum BCVA was obtained)
  - The second stage is from Month 2 through Month 6 to see if the benefit is maintained with quarterly treatment
  - The third stage is from Month 5 through Month 12 when therapy is given on a PRN basis
  - There are two phase 3 studies: each with 460 patients with approximately equal numbers with BRVO and CRVO
Design for Phase 3 Clinical Trials

**Combination arm**: suprachoroidal CLS-TA + Intravitreal aflibercept; Q12Wk

**Control arm**: Intravitreal aflibercept; Q4Wk
Protocol discussion – Stage 1

**Combination arm:** suprachoroidal CLS-TA + Intravitreal aflibercept; Q12Wk

**Control arm:** Intravitreal aflibercept; Q4Wk

Conceptually there are three portions to the phase 3 design

**Stage 1:** Through Month2 [Week 8]
Does CLS-TA given in combination with intravitreal aflibercept contribute to an earlier beneficial outcome in RVO patients?
Protocol discussion – Stage 2

**Combination arm**: suprachoroidal CLS-TA + Intravitreal aflibercept; Q12Wk

**Control arm**: Intravitreal aflibercept; Q4Wk

**Stage 2**: Week 8 through Week 24

Are the outcomes seen through Month 2 *maintained through Month 6* using a quarterly combination dosing regimen?

*Day 0, Wk 4, Wk 8, Wk 12, Wk 16, Wk 20*

2 Month primary efficacy endpoint
Protocol discussion – Stage 3

**Combination arm:** suprachoroidal CLS-TA + Intravitreal aflibercept; Q12Wk

- Day 0
- Wk 4
- Wk 8
- Wk 12
- Wk 16
- Wk 20
- Wk 24
- Wk ww
- Wk xx
- Wk yy
- Wk zz

**Suprachoroidal CLS-TA + Intravitreal aflibercept**

- Enrollment

Day 0
- Wk 4
- Wk 8
- Wk 12
- Wk 16
- Wk 20
- Wk 24
- Wk ww
- Wk xx
- Wk yy
- Wk zz

**Control arm:** Intravitreal aflibercept; Q4Wk

- Day 0
- Intravitreal aflibercept
- Intravitreal aflibercept
- Intravitreal aflibercept
- Intravitreal aflibercept
- Intravitreal aflibercept
- Intravitreal aflibercept
- Intravitreal aflibercept
- Intravitreal aflibercept

**Stage 3:** Month 6 through the end of the study

How long does treatment last following dosing at Month 6?
Thank You