Advances in Retinal Drug Delivery:

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Disclosure

• Founder/inventor ForSight Labs Vision 4

Lucentis (monthly)

• 500 ug
• Half life 8-9 days
• Cmax- 100 ug/mL (vitreous concentration)
• Cmin- 10 ug/mL at the end of 30 days
• Cmin- 1 ug/mL at 60 days!

• If we could deliver “only the minimum dose” then 500 ug would be a 6 month dose!

Drug Delivery is part of the Future

• Every Major Pharma has identified Drug Delivery as a part of the future of treatment of Retinal Disease
• Retisert, Ozurdex, Iluvien
  — Steroid based
  — IOP elevations but strong effects on retinal disease
• Santen Siralonus
• Puida/Pfizer and Neuron
• Clearside
  — Suprachoroidal Steroid
• Protein Drug Delivery will be a key part of the future
  — Several start up efforts
  — Graybug, Ocular Therapeutics
  — Genentech/Vision 4
• Topical Approaches "may" be possible
  — The i
Anti-VEGF sustained delivery
Large and Small molecules

- Micro-particles and Gels
  - Well known biodegradable platform
    - Being developed by Ocular Therapeutics and GrayBug
  - Advantages
    - Injectable
  - Disadvantages
    - Duration of polymer longer than drug
    - Particles may be visible

Neurotech ECT
Targets:
MacTel
CNTF may slow vision loss

MacTel-NeuroTech

- Interim results appear encouraging

- Glial protection.

Steroids

- Triamcinolone Acetinide
  - Insoluble (low rate of solubility)
  - Provides its own “depot”
  - Biphasic elimination
    - Rapid and then slower
Retisert, Bausch & Lomb

- FDA approved - fluocinolone acetonide delivery for uveitis
- FDA approved “Vitrasset” - ganciclovir delivery for CMV retinitis

**Advantages**
- zero order release kinetics
- delivers drug up to 3 yrs

**Disadvantages**
- requires surgical implantation and removal
- not dose titratable
- 100% cataract
- ~40% trabeculectomy for increased IOP

Alimera

- Non-biodegradable Injectible
- Two year DME study 956 patients (FAME)
- 26-31% 15 letter improvements
- IOP rise (> 30 mm Hg)
- 16-30% patients
- Trabeculectomy 2-5%

Allergan Ozurdex

- OZURDEX (Allergan)
  - CRVO and BRVO
  - 0.7 mg
  - Doubled “15 letter gainers”
  - 12% (control) to 24% (treated)
  - 3 months
  - 25% Increased IOP

Clearside Biomedical

- Supra-choroidal placement
- Directs drug to the Choroid and posterior retinal
Supra-choroidal steroid for RVO

- Anti-VEGF improves vision over observation
- CLS-1003-201
  - aflibercept vs Supra CLS-TA+aflibercept
    - (23 patients each arm)
  Showed reduction in # of injections
  16 injections vs 5 injections  P=0.003
  Improved vision
  +11.3 letter vs 18.9 letters (+7.6 in combo)
  Less edema on OCT
  384 vs 285 at 3 months

In CATT, PRN regimen gave good results but not as good as monthly, and necessitated multiple injections

Port Delivery System

Injectable Reservoir
Targets 4-6 months Release

Mean Number of Injections at 12 Months in AMD trials
Background

• Thus, a sustained delivery device is well needed and may be extremely beneficial
  – Delivering constant drug levels for a prolonged period of time
  – Avoiding need for repeat injections

Study Design

• Single-Center, Uncontrolled Study
• 20 Treatment Naïve Wet AMD Patients
• Implant Placement on Study Day 0
• Implant Refill Eligibility Evaluated Monthly Based Upon Predetermined Criteria
• Study duration: 12 Months

Tolerability of Device and Refill Procedure

<table>
<thead>
<tr>
<th>2 Week Visit</th>
<th>6 Month Visit (1 month post-refill)</th>
<th>12 Month Visit (1 month post-refill)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
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</tbody>
</table>

Patient 101
Treatment Summary

- **96 total implant refills**
- **Patients with vitreous hemorrhage refilled monthly (through months 10 and 11)**
- **Mean time to first implant refill eligibility: 3.8 months, range 1-11 months**
- **Mean 4.2 refills in remaining 18 Patients**

12 months BCVA
Categorical Change in Vision

![Graph showing categorical change in vision](image)

Mean Change in BCVA from Baseline

![Graph showing mean change in BCVA](image)

Change in CNV Leakage Area

![Graph showing change in CNV leakage area](image)
Safety of Device Removal
Explanation Related Adverse Events
(6 Patients/Procedures)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Number of Patients with ≥1 event</th>
<th>Severity</th>
<th>Time to Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyphaema</td>
<td>1 (17%)</td>
<td>Mild</td>
<td>3 days</td>
</tr>
<tr>
<td>Conjunctival haemorrhage</td>
<td>1 (17%)</td>
<td>Mild</td>
<td>3 days</td>
</tr>
<tr>
<td>Conjunctival hyperaemia</td>
<td>1 (17%)</td>
<td>Mild</td>
<td>7 days</td>
</tr>
</tbody>
</table>

Patient 103

Patient 113

LADDER

• Genentech Phase 2
  – 220 patients with newly diagnosed CNV AMD
  – 3 dosages compared to monthly Lucentis
  – Double blind
    • Primary endpoint:
      – Time to refill injection
    • Secondary endpoints
      – Mean change BCVA and CFT
      – Adverse events