Treatments on the Horizon

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Latanoprostene bunod (Vesneo)

- Valeant (B+L)
- Nitrous oxide-donating prostaglandin F2-alpha analogue that reduces IOP
- When exposed to ubiquitous esterases in the ocular environment, is cleaved into latanoprost acid, a prostaglandin F2alpha receptor agonist, and butanediol mononitrate, a nitric oxide (NO)-donating moiety

LBN

- NO donors relax the trabecular meshwork (TM) and increase aqueous humour outflow.
- They activate the large conductance calcium-activated potassium channel, or BKCa ion channel, involved in reducing TM cell volume.
- NO donors may trigger, among other things, reduction of actomyosin contractility and disassembly of the actin cytoskeleton and cell adhesion system in the cells of the conventional outflow pathway, causing cell shape changes and overall relaxation of the TM and inner wall of Schlemm’s canal leading to decreased resistance to aqueous humour outflow.
- Increasing the conventional outflow of aqueous through the TM results in better IOP lowering than that of latanoprost alone.

Mean diurnal intraocular pressure (IOP) at baseline and on Day 28 (intent-to-treat population). *p=0.005 versus latanoprost; †p=0.009 versus latanoprost.


A Randomized, controlled comparison of latanoprostene bunod and latanoprost 0.005%: Voyager Study

<table>
<thead>
<tr>
<th>Systemorgan class</th>
<th>LBN 0.005% (n=48)</th>
<th>LBN 0.012% (n=48)</th>
<th>LBN 0.048% (n=48)</th>
<th>LBN 0.048% (n=48)</th>
<th>Latanoprost 0.005% (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of subjects with ≥1 TEAE</td>
<td>20 (41.7)</td>
<td>18 (37.5)</td>
<td>20 (41.7)</td>
<td>18 (37.5)</td>
<td>19 (35.2)</td>
</tr>
<tr>
<td>No of subjects with ≥1 treatment-related TEAE</td>
<td>17 (35.4)</td>
<td>18 (37.5)</td>
<td>16 (33.3)</td>
<td>19 (35.2)</td>
<td>15 (27.8)</td>
</tr>
</tbody>
</table>

• The pivotal Phase 3 program includes two separate randomized, multicenter, double-masked, parallel-group clinical studies, APOLLO and LUNAR, designed to compare the efficacy and safety of VESNEO™ administered once daily (QD) against timolol maleate 0.5% administered twice daily (BID) in lowering IOP in patients with open-angle glaucoma or ocular hypertension.

• The primary endpoint of both studies, which include a combined total of 840 patients, was the reduction in mean IOP measured at specified time points during three months of treatment.

• The collection of patient safety data for a total of up to 12 months is still ongoing.

• The primary endpoint of non-inferiority to timolol maleate 0.5% was achieved in both Phase 3 studies.

• VESNEO™ showed a reduction in mean IOP of 7.5 to 9.1 mmHg from baseline between 2 and 12 weeks of treatment in the two Phase 3 studies.

• This IOP effect was statistically superior (p < 0.05) to timolol in both studies.

• VESNEO™ also showed positive results on a number of secondary endpoints.

• There were no significant safety findings in either study.

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**Rhopressa™**

- Aerie Pharmaceuticals
- Once-daily
- Inhibits Rho Kinase (ROCK)
- Inhibits norepinephrine transporter (NET)
- Novel biochemical targets for lowering IOP

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**Mechanisms of Action for Rhopressa**

- Rhopressa™ reduces IOP via three separate MOAs:
  1. Through ROCK inhibition, it increases fluid outflow through the trabecular meshwork which accounts for approximately 80% of fluid drainage from the eye
  2. Reduces episcleral venous pressure: the pressure of the blood in the episcleral veins of the eye where eye fluid drains into the bloodstream
  3. Through norepinephrine transporter inhibition, it reduces the production of aqueous.

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**Rho Kinase Inhibitors**

- These selective agents work by relaxing the trabecular meshwork through inhibition of the actin cytoskeleton contractile tone of smooth muscle.
- This results in increased aqueous outflow directly through the trabecular meshwork, achieving lower intraocular pressures in a range similar to prostaglandins.
- There are also animal studies indicating that ROCK inhibitors may improve blood flow to the optic nerve, increase ganglion cell survival, and reduce bleb scarring in glaucoma surgery

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**Phase 2b Clinical Trial**

- Once-daily Rhopressa™ demonstrated mean IOP reductions of 5.7 and 6.2 mmHg on days 28 and 14, respectively.
- What does this mean clinically?
  - EMGT demonstrated a sustained 5 mmHg reduction in IOP reduces risk of disease progression by approximately 50%
Phase 3 Registration Trials for Rhopressa

Rocket 1 Study
- Compared 182 Rhopressa™ qd patients to 188 timolol bid patients
- Baseline IOP 20-27mmHg
- Results showed loss of efficacy at week 6 and on day 90 in ~20% of Rhopressa arm
- Hyperemia in 35% of patients
  - 80% reported it as "mild"

Rocket 2 Study
- Baseline IOP 20-22mmHg
- Why?
- In Rocket 1, this range of IOP had better IOP lowering success that those above 25.
- Results of Rocket 2 not yet available

Roclatan™

- Aerie Pharmaceuticals
- Single-drop, fixed combination with "quadruple-action"
  - Rhopressa
    - Triple MOA
      - Increased outflow through TM
    - Decreased episcleral venous pressure
    - Decreased aqueous production
  - Latanoprost
    - Primary MOA
      - Increase uveoscleral outflow

Mean±SEM.

Proportion of patients with mean diurnal intraocular pressure reduced to ≤15, 16, 17 or 18 mm Hg at day 29.

### Fixed-dose combination of AR-13324 and latanoprost: a double-masked, 28-day, randomised, controlled study in patients with open-angle glaucoma or ocular hypertension

#### Table 2

<table>
<thead>
<tr>
<th>System organ class (SOC)</th>
<th>AR-13324 2% (N=90)</th>
<th>AR-13324 0.01% (N=89)</th>
<th>Latanoprost 0.005% (N=90)</th>
<th>Lowered mean IOP (P)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td>39 (43.3)</td>
<td>36 (39.3)</td>
<td>34 (37.7)</td>
<td>0.126</td>
<td>0.935***</td>
</tr>
<tr>
<td>Cardiac hypertrophy</td>
<td>3 (3.3)</td>
<td>3 (3.3)</td>
<td>3 (3.3)</td>
<td>0.809</td>
<td>0.809</td>
</tr>
<tr>
<td>Diastolic hypertension</td>
<td>1 (1.1)</td>
<td>1 (1.1)</td>
<td>2 (2.2)</td>
<td>0.172</td>
<td>0.809</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (1.1)</td>
<td>1 (1.1)</td>
<td>2 (2.2)</td>
<td>0.172</td>
<td>0.809</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (1.1)</td>
<td>1 (1.1)</td>
<td>2 (2.2)</td>
<td>0.172</td>
<td>0.809</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1 (1.1)</td>
<td>1 (1.1)</td>
<td>1 (1.1)</td>
<td>0.448</td>
<td>0.322***</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (1.1)</td>
<td>1 (1.1)</td>
<td>1 (1.1)</td>
<td>0.448</td>
<td>0.322***</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1 (1.1)</td>
<td>1 (1.1)</td>
<td>1 (1.1)</td>
<td>0.448</td>
<td>0.322***</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1 (1.1)</td>
<td>1 (1.1)</td>
<td>1 (1.1)</td>
<td>0.448</td>
<td>0.322***</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (1.1)</td>
<td>1 (1.1)</td>
<td>1 (1.1)</td>
<td>0.448</td>
<td>0.322***</td>
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**Roclatan™**

- **Phase 2b Clinical Trial**
  - 297 patients
  - Mean baseline=25.1mmHg
  - Lowered mean IOP by 34% to mean 16.5mmHg
  - Roclatan mean IOP reduction was ~2mmHg greater than the IOP reduction with latanoprost alone.
- **Phase 3 trial (Mercury 1) expected to begin end 2015.**

**Bimatoprost SR**

- **Allergan Pharmaceuticals**
- Sustained release implant
- Biodegradable, preservative-free implant preloaded into a single use applicator
- Bimatoprost SR is placed in the anterior chamber
- The drug is slowly released for about 3 to 4 months and the implant slowly dissolves in about 12 to 15 months.
- As of April, 2014, a total of 87 patients had received a single administration and of those, 12 had received a repeat administration of Bimatoprost SR on the 192024-041D study.
**Sustained-release travoprost (OTX-TP)**

- Ocular Therapeutics
- Intracameral depot composed of polyethylene glycol hydrogel and drug containing micro-particles
  - Sustain release travoprost punctal plug
- Phase 2 clinical trials underway

**Trabodenoson**

- Inoteck
- a potent and highly selective adenosine mimic acting only at the A1 receptor subtype
- In Phase 2 trials, treatment with trabodenoson was shown to significantly reduce IOP in glaucoma and OHT patients and was well-tolerated.
- After 28 days of trabodenoson monotherapy, the IOP-lowering efficacy achieved was in the range of the market leading prostaglandins (e.g., latanoprost).

**MATRx-1 (trabodenoson)**

- MATRx-1 is a Phase 3 randomized, double-masked, placebo-controlled trial of trabodenoson in approximately 335 patients diagnosed with primary open-angle glaucoma (POAG) or ocular hypertension (OHT).
- Goal:
  - Assess the efficacy, safety and tolerability of trabodenoson over three months of treatment.
  - The primary endpoint will be the reduction of intraocular pressure (IOP) as compared to the placebo treatment arm. In addition, the study will contain a timolol 0.5% arm to validate the sensitivity of the patient population.
  - Intraocular pressure (IOP) will be measured at four timepoints during the day, 8AM, 10AM, 12PM, and 4PM on days 14, 28, 42, and 84. Three doses of trabodenoson will be administered: 1000 mcg once daily, 1500 mcg twice daily, and 2000 mcg once daily.
  - The trial will enroll patients with IOP greater than or equal to 24 mm Hg and less than or equal to 34 mm Hg.

**OTX-TP Phase 2a Study Results**

**OTX-TP Comparison to Timolol and Placebo Plug**

Mean 8:00 AM Reduction from Baseline

**Product Name** | **Company** | **Type of Drug** | **MOA** | **Status**
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Latanoprost bunod (Vesneo) | Valeant (B+L) | Nitric oxide-donating PG F2-a analog | Increases outflow through TM | NDA Submitted to FDA
Rhopressa | Aerie | Inhibit Rho kinase and norepinephrine transported | Increase TM outflow; reduce episcleral venous pressure; reduce production | Phase 3
Roclatan | Aerie | Combo Rhopressa + latanoprost | Rhopressa MOA and increased uveoscleral outflow | Phase 3
Bimatoprost SR | Allergan | Sustained release prostinal implant | Increase uveoscleral outflow | Phase 3
Trabodenoson | Inoteck | Selective adenosine mimetic acting at A1 receptor subtype | Increase TM outflow by increase uptake of Proteases | Phase 3