PAN-90806: Once-daily topical anti-VEGF eye drop for wet AMD and other neovascular eye disease

OIS@AAO 2019
Potent anti-VEGF pharmacology and the right physical chemistry enables delivery to central choroid and central retina with topical administration.

### Inhibition of VEGF Signaling

<table>
<thead>
<tr>
<th>Current Treatments</th>
<th>PAN-90806</th>
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<tbody>
<tr>
<td>Anti-VEGF Biologics</td>
<td>PAN-90806 VEGFR2 TKI</td>
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</tbody>
</table>

**VEGF**

**VEGFR2 TKI**

**VEGF Receptor**

**PAN-90806**

### Delivery to Target Tissues

*Trans-scleral vascular route to reach target tissues*
Previous Ph 1/2 trials confirmed anti-VEGF biological signal with QD topical dosing:
• As monotherapy in nAMD patients over 8 weeks of treatment (n=20)
• As maintenance therapy in nAMD following a single injection of ranibizumab over 12 weeks (n=10)
• As monotherapy in PDR+/- DME over 8 weeks (n=10)

These studies also identified reversible punctate keratopathy due to off-target inhibition of corneal epithelial EGFR (IOVS 2016;57:5864)

PanOptica developed a new, patented suspension formulation with an improved safety and tolerability profile in non-clinical primate studies for further development

Now, for the rest of the story...
PAN-01-102: Objectives for Ph1/2 nAMD Trial with PAN-90806 Suspension

Solidify the rationale for late-stage development as a potential maintenance therapy alongside intravitreal standard of care by achieving the following:

1. Confirmation of clinical safety & tolerability for once-daily eyedrop at expanded dose range as monotherapy over three months

2. Demonstration of anti-VEGF biological response with eyedrops alone
   1. Clinical improvement in structure / function in treatment naïve pts w/nAMD OR
   2. Clinical stability in structure/function
   3. Avoidance of need for rescue with intravitreal anti-VEGF (Lucentis®)
Randomized, double-masked, dose-ranging, Phase 1/2 monotherapy study in treatment naïve nAMD patients with PAN-90806 suspension

Endpoints / Objectives

**Primary**

**Safety / Tolerability**

**Secondary**

Anti-VEGF Biological Response

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**PAN-01-102 Protocol**

**Monotherapy Only (51 patients for 12 weeks, follow up to 16 weeks)**

Week -1 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12

Screening

51 Patients Randomized to Dose (1:1:1)

- Daily 10 mg/mL QD (n = 17)
- Daily 6 mg/mL QD (n = 18)
- Daily 2 mg/mL QD (n = 16)

Rescue injections allowed beginning Week 2
Specific criteria, Reading Center confirmed

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STRICTLY CONFIDENTIAL
PAN-01-102 Primary Objective: Safety

Final independent DSMC safety assessment week 12 (last on-treatment visit)

No significant drug-related safety concerns or trends in PAN-01-102

Conclusions stated by the SMC following final review of all safety data for all 51 patients:

“No major or serious untoward (unfavorable and unintended) safety issues or trends were observed....

PAN-90806 ophthalmic suspension, administered once-daily at concentrations of 2 mg/ml, 6 mg/ml, and 10 mg/ml, is reasonably safe and well-tolerated in treatment-naive patients with neovascular age-related macular degeneration.”

PAN-90806 Suspension demonstrated significantly improved safety & tolerability compared to the prior (solution) formulation
PAN-01-102 Secondary Objective: anti-VEGF Biological Response

A topical eye drop demonstrated anti-VEGF biological response at all doses (2 mg/mL, 6 mg/mL, 10 mg/mL) in treatment naïve wet AMD patients as once daily monotherapy.

- 51% of patients completed the study on PAN-90806 eyedrops alone – never rescued through the 1 month post-treatment (week 16) visit.
- 23 of 26 (88%) non-rescued patients showed clinical improvement or stability based on independent masked review by panel of retina experts.
PAN-01-102: Examples of clinical improvement on monotherapy

**Type 2 lesion**
2 mg/ml
112 µM ↓ CST
5 letter gain

**Type 1 lesion**
6 mg/ml
142 µM ↓ CST
26 letter gain
PAN-01-102: Pharmacodynamic activity occurs in 4-6 weeks
10mg/mL Pt: 6 letter gain / 142 micron reduction CST (Week 12)
Rescued patients had thicker retinas and worse VA at baseline vs those never rescued or rescued late

Patients rescued earliest (≤ 4 wk) had baseline CST 113µm higher than never rescued pts

<table>
<thead>
<tr>
<th>Time of 1st Injection based on OCT at</th>
<th>Number of Pts</th>
<th>Baseline CST (Day 1) Mean</th>
<th>Snellen VA</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 4 weeks</td>
<td>13</td>
<td>444 µm</td>
<td>20/100</td>
</tr>
<tr>
<td>&gt; 4 &lt; 8 weeks</td>
<td>0</td>
<td>365 µm</td>
<td>20/80</td>
</tr>
<tr>
<td>8 to 12 weeks</td>
<td>10</td>
<td>365 µm</td>
<td>20/80</td>
</tr>
<tr>
<td>&gt; 12 weeks</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Rescued Pts</td>
<td>25</td>
<td>406 µm</td>
<td>20/80</td>
</tr>
<tr>
<td>All Non-Rescued Pts</td>
<td>26</td>
<td>331 µm</td>
<td>20/63</td>
</tr>
<tr>
<td>All Patients</td>
<td>51</td>
<td>368 µm</td>
<td>20/80</td>
</tr>
</tbody>
</table>
PAN-01-102: Biological Activity is also Confirmed by Patient Stability in Non-Rescued Patients through week 16 (one month post tx)

Mean Change from Baseline (Day 1)

SD-OCT CST

Mean Change from Baseline +/- SE (μM)

ETDRS BCVA

Mean Change from Baseline +/- SE (letters)

Drops D/C’d

Day 1 Week 2 Week 4 Week 8 Week 12 Week 16

Mean Change from baseline +/- SE (μM)

Mean Change from baseline +/- SE (letters)

Drops D/C’d

Day 1 Week 2 Week 4 Week 8 Week 12 Week 16
nAMD Natural History shows mean VA loss at of 5-15 letters with 50% of patients progressing to legal blindness at 3 months

The Natural History and Prognosis of Neovascular Age-Related Macular Degeneration

A Systematic Review of the Literature and Meta-analysis

Ophthalmology 2008 (115):116-26
4300+ patients meta-analysis
Baseline VA 20/87

Outcome 3 months

- <3: 76.0 (69.0-82.3)
- ≥3–≤6: 14.1 (10.5-18.2)
- >6: 10.1 (6.0-15.1)

≥3 lines = 24%

Figure 1. Mean visual acuity (VA) change (logarithm of the minimum angle of resolution). t = no. of studies in meta-analysis.
Patients avoided 79% of possible injections compared with on-label monthly injection regime (all 51 patients)

<table>
<thead>
<tr>
<th>Subjects with at least 1 Ranibizumab injection</th>
<th>2mg/ml N=17</th>
<th>6mg/ml N=18</th>
<th>10mg/ml N=16</th>
<th>Total N=51</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 (41.2%)</td>
<td>9 (50.0%)</td>
<td>9 (56.3%)</td>
<td>24 (49.0%)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean number of Ranibizumab injections given per patient</th>
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<tbody>
<tr>
<td>0.82</td>
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<table>
<thead>
<tr>
<th>Mean number of Ranibizumab injections avoided per patient</th>
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<tbody>
<tr>
<td>3.18</td>
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</table>

<table>
<thead>
<tr>
<th>Total number of Ranibizumab injections avoided in all patients</th>
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<tr>
<td>54 (79.4%)</td>
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</table>
PAN-01-102: Independent Masked Retina Expert Review

• For the first time, a topical anti-VEGF eyedrop has demonstrated both safety and biological response in treatment naïve wet AMD patients as monotherapy.

• 51% of PAN-01-02 patients completed the study on PAN-90806 eyedrops alone through week 16 (drops were d/c’d after week 12).

• Masked KOL review suggests study entry criteria VA (<20/50) and baseline severity (e.g. CST > 400uM) predisposed patients to early rescue.

The P1/2 trial data supports advancing the drug into clinical studies to assess its potential benefit in nAMD, DME, RVO, prophylaxis, and chronic maintenance.
PAN-90806: a potential game changer in wet AMD by creating a new paradigm to address adherence, undertreatment, & loss to follow-up

### Potential Future Treatment Paradigm

<table>
<thead>
<tr>
<th>Loading Dose</th>
<th>Ongoing Treatment</th>
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<tbody>
<tr>
<td>Month</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
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<td>7</td>
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<td></td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>12</td>
</tr>
</tbody>
</table>

- **Loading Dose**: 1st 3 months
- **Ongoing Treatment**: Months 4 to 12

#### Future Paradigm

- **Daily PAN-90806 Maintenance Therapy**
- **Injections on a need-only basis**

Imagine a “treat-and-extend” regimen with the benefit of continuous VEGF suppression using a self-administered once-daily eyedrop.
PanOptica has a strong intellectual property portfolio with newly issued, pending and planned patents expiring ≥ 2034

Delivery to back of the eye requires ability to deliver high concentration to choroid/retina as well as reduce or eliminate off-target corneal AEs

Global Rights to All Ophthalmic Indications

- Licensed extensive portfolio of issued patents from OSI/Astellas out of a Pfizer cancer devt collaboration

New IP from Original PanOptica Inventions

- USA: 6 Granted, 3 Pending Patents
- OUS: 31 Granted Patents, including AU, EU & JP
- 31 Pending, Incl AU, CA, CN, EU, JP, KR
- Pursuing additional patents for other discoveries
PanOptica is led by individuals with extensive ophthalmology research, development, and commercial experience

**PanOptica Leadership**

**Paul G. Chaney**
President & CEO
Former President of OSI Eyetech with 35+ years experience and 20+ in ophthalmology

**Martin B. Wax, MD**
CMO & EVP of Dev.
Former VP of R&D at Alcon who led dev. in retina, dry eye, and glaucoma (over 200 publications)

**Kristine Curtiss**
ED, Clinical Operations
Previously Dir. Clinical Affairs at Opko and Oraya with 20+ years of clinical trial experience

**Lori Forrest**
ED, Finance & Controller
Former controller at Helsinn Therapeutics with 20+ years of acct. experience in pharmaceuticals

**David Bingaman, DVM, ACVO, PhD**
Head, Retina Dev.
Former Director of Retina R&D at Alcon with 20+ years of experience in ophthalmology

**Angela Kothe, OD, PhD**
Consultant, Reg. Affairs
VP of Silver Pharma Consulting with 25+ years of regulatory experience
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