PANOPTICA

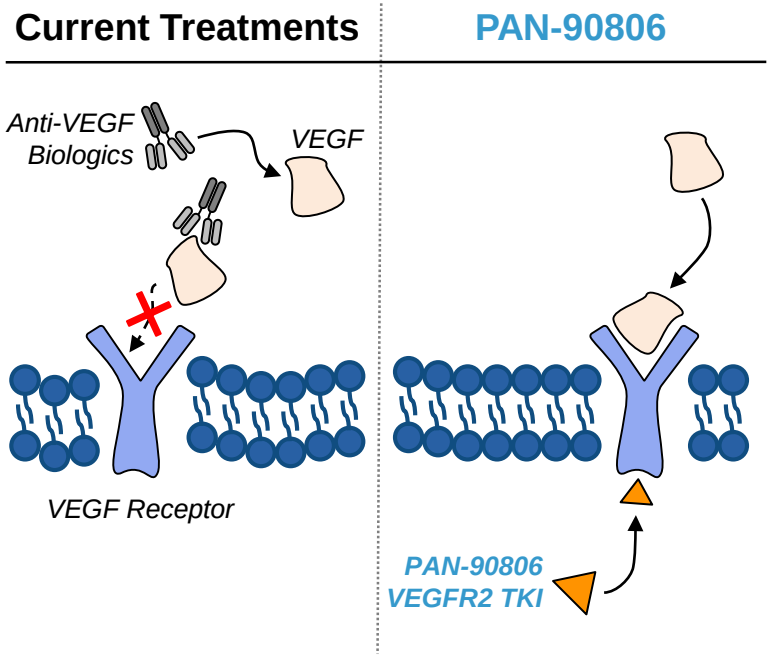
PAN-90806: Once-daily topical anti-VEGF eye drop for wet AMD and other neovascular eye disease

OIS@AAO 2019

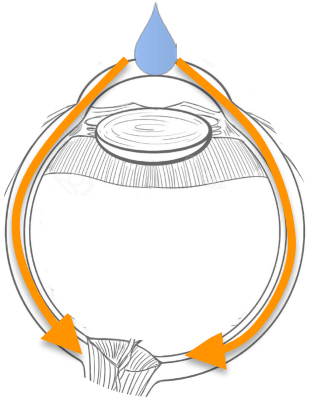
Potent anti-VEGF pharmacology and the right physical chemistry enables delivery to central choroid and central retina with topical administration

ILLUSTRATIVE

Inhibition of VEGF Signaling



Delivery to Target Tissues



Trans-scleral vascular route to reach target tissues

PAN-90806 Development History with abandoned solution formulation

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

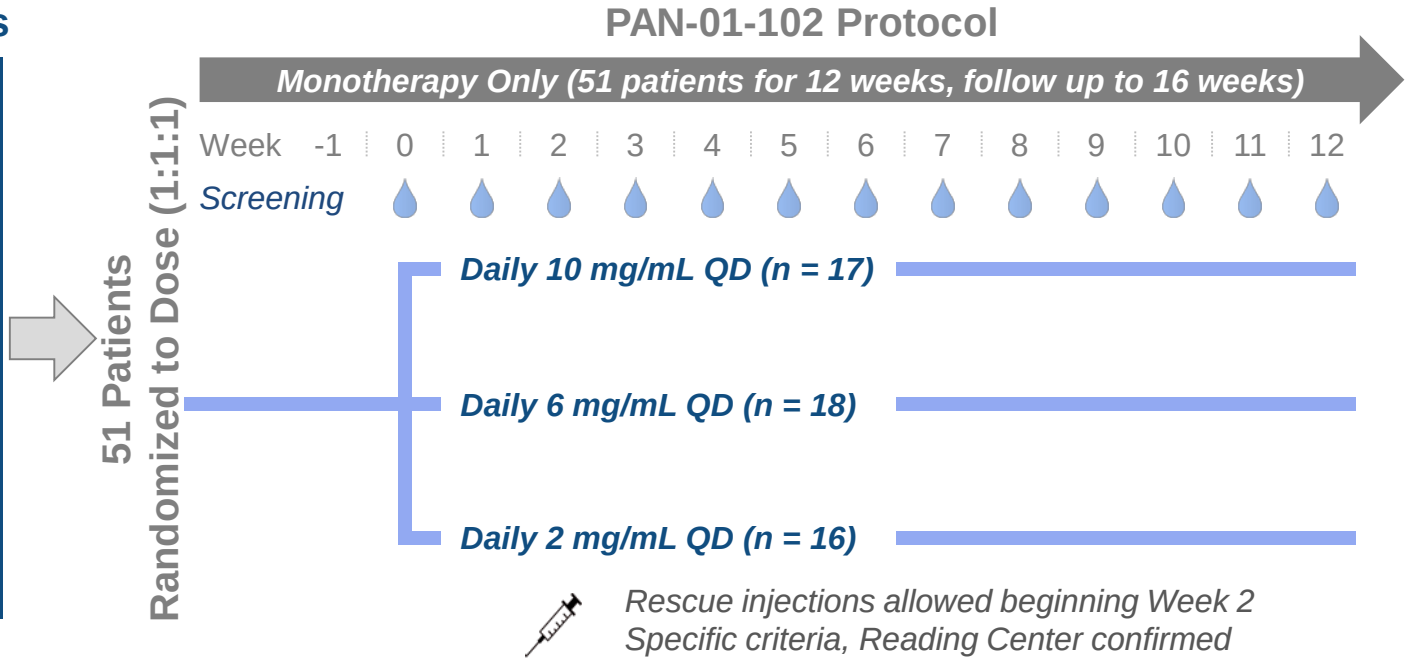
Endpoints / Objectives

Primary

Safety / Tolerability

Secondary

Anti-VEGF Biological Response



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."

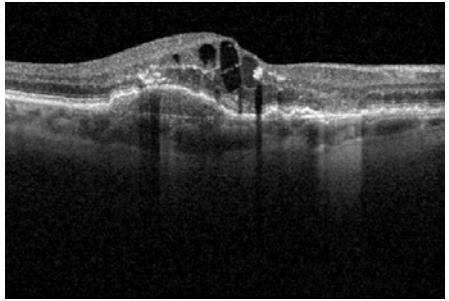
PAN-90806 Suspension demonstrated significantly improved safety & tolerability compared to the prior (solution) formulation

PAN-01-102 Secondary Objective: anti-VEGF Biological Response

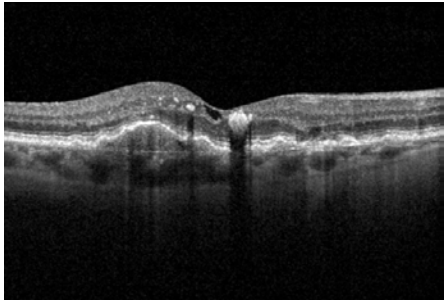
A topical eye drop demonstrated anti-VEGF biological response at all doses (2 mg/mL, 6 mg/mL, 10 mg/mL) in treatment naïve wet AMD patients as once daily monotherapy

- **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**

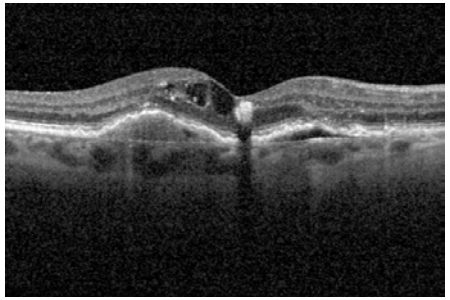
PAN-01-102: Examples of clinical improvement on monotherapy



Day 1
CST: 395 VA: 61



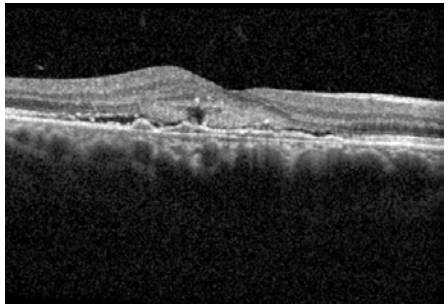
Week 12
CST: 283 VA: 66



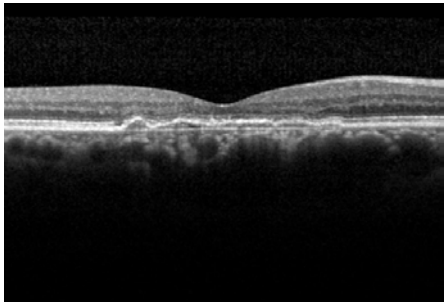
1 Month Post Tx Follow-up
CST: 328 VA: 65

Type 2 lesion
2 mg/ml

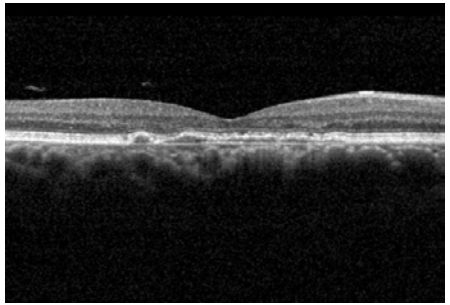
112µM ↓ CST
5 letter gain



Day 1
CST: 298 VA: 44



Week 12
CST: 156 VA: 70



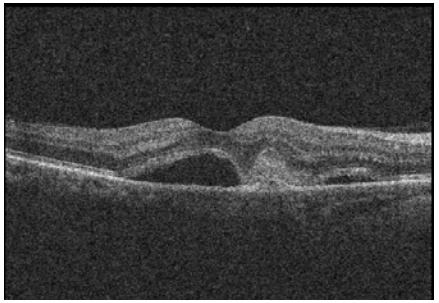
1 Month Post Tx Follow-up
CST: 156 VA: 70

Type 1 lesion
6 mg/ml

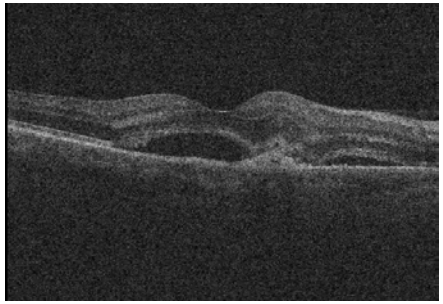
142µM ↓ CST
26 letter gain

PAN-01-102: Pharmacodynamic activity occurs in 4-6 weeks

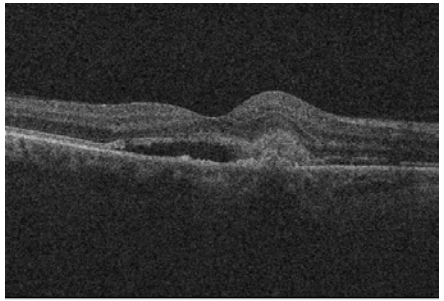
10mg/mL Pt: 6 letter gain / 142 micron reduction CST (Week 12)



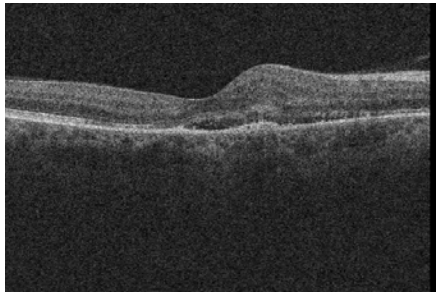
Day 1
CST: 423 VA: 67



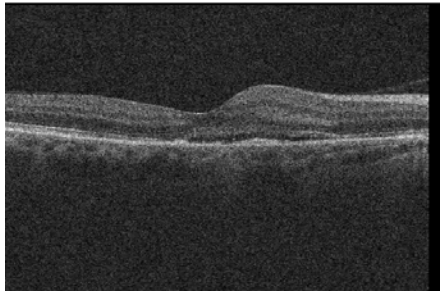
Week 4
CST: 387 VA: 75



Week 8
CST: 350 VA: 68



Week 12
CST: 281 VA: 73



1 Mo Post Tx Follow-up
CST: 258 VA: 78

Rescued patients had thicker retinas and worse VA at baseline vs those never rescued or rescued late

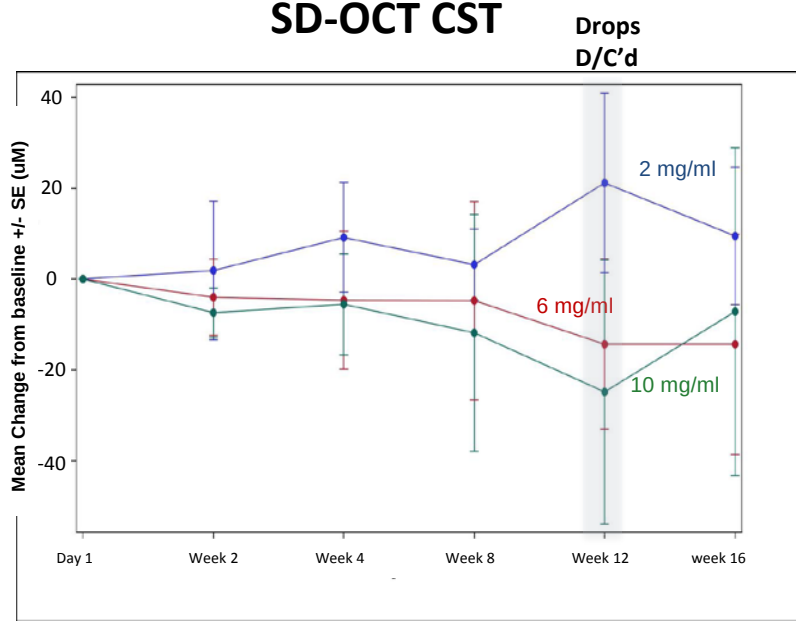
Patients rescued earliest (≤ 4 wk) had baseline CST 113µm higher than never rescued pts

Time of 1st Injection based on OCT at	Number of Pts	Baseline CST (Day 1) Mean	Snellen VA
≤ 4 weeks	13	444 µm	20/100
> 4 < 8 weeks	0	365 µm	20/80
8 to 12 weeks	10		
> 12 weeks	2		
All Rescued Pts	**25**	**406 µm**	20/80
All Non-Rescued Pts	**26**	**331 µm**	20/63
All Patients	**51**	**368 µm**	20/80

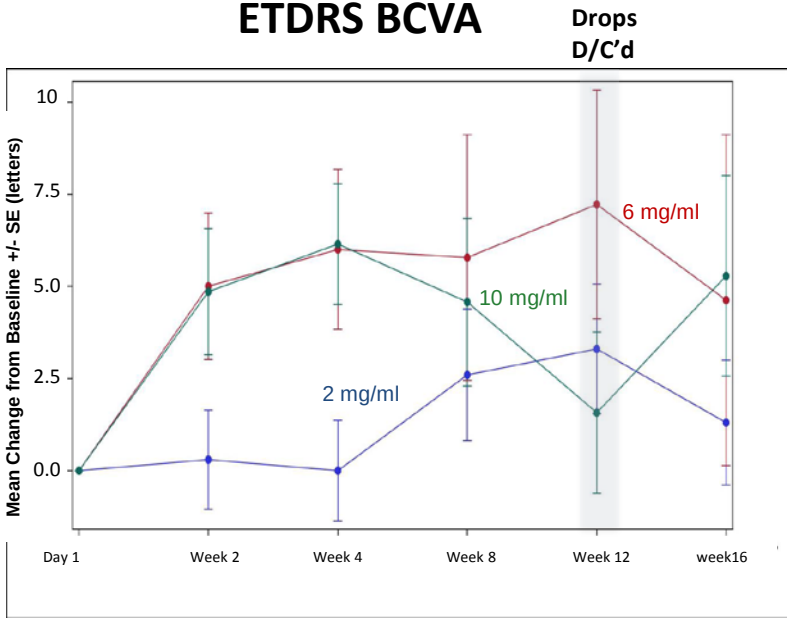
PAN-01-102: Biological Activity is also Confirmed by Patient Stability in Non-Rescued Patients through week 16 (one month post tx)

Mean Change from Baseline (Day 1)

SD-OCT CST



ETDRS BCVA



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

Tien Wong, MD, PhD,[1] Usha Chakravarthy, MD, PhD,[2] Ronald Klein, MD, MPH,[3] Paul Mitchell, MD, PhD,[4] Gergana Zlateva, PhD,[5] Ronald Buggage, MD,[5] Kyle Fahrbach, PhD,[6] Corey Probst, BS,[6] Isabella Sledge, MD, MPH[6]

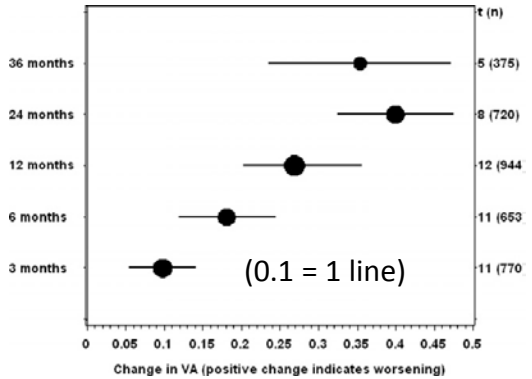


Figure 1. Mean visual acuity (VA) change (logarithm of the minimum angle of resolution). t = no. of studies in meta-analysis.

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

Outcome	3 months
VA lines lost	
<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%

Patients avoided 79% of possible injections compared with on-label monthly injection regime (all 51 patients)

Mean number of rescues per patient <1 (all patients)

	2mg/ml N=17	6mg/ml N=18	10mg/ml N=16	Total N=51
Subjects with at least 1 Ranibizumab injection	7 (41.2%)	9 (50.0%)	9 (56.3%)	24 (49.0%)
Mean number of Ranibizumab injections given per patient	0.82	0.83	0.81	0.84
Mean number of Ranibizumab injections avoided per patient	3.18	3.17	3.19	3.18
Total number of Ranibizumab injections avoided in all patients	54 (79.4%)	57 (79.2%)	51 (79.7%)	162 (79.4%)

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**

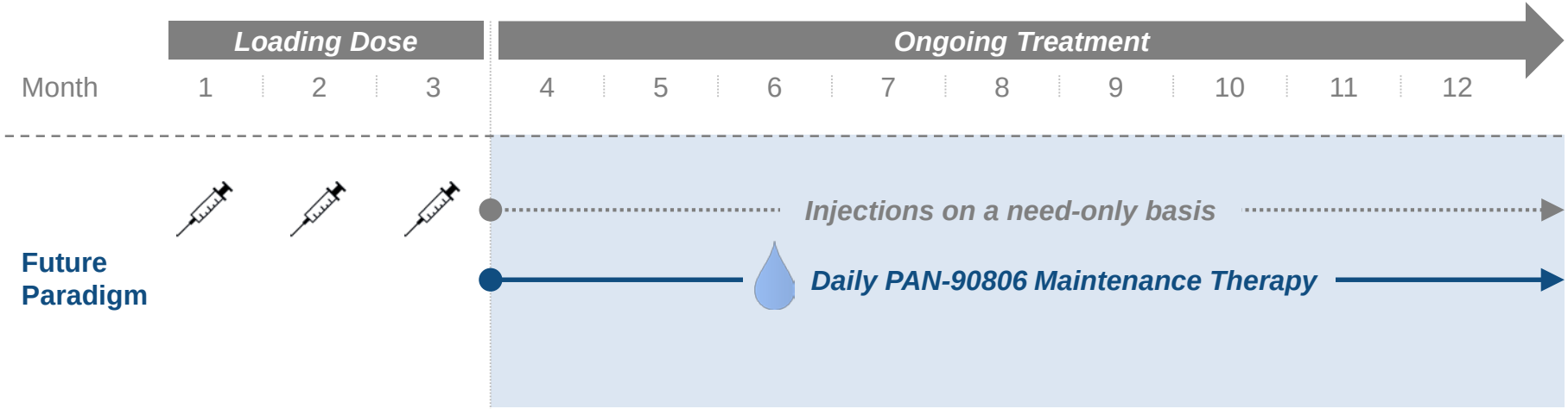
- 51% of PAN-01-02 patients completed the study **on PAN-90806 eyedrops alone through week 16** (drops were d/c'd after week 12)

- 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



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

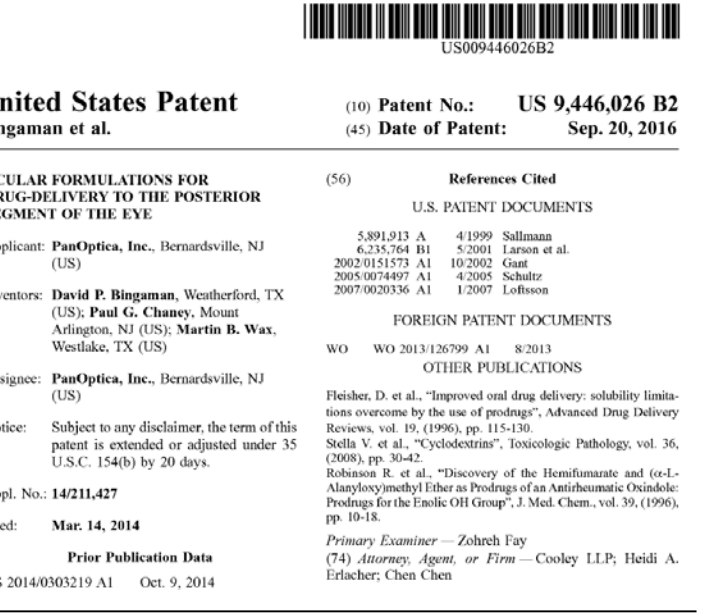
Delivery to back of the eye requires ability to deliver high concentration to choroid/retina as well as reduce or eliminate off-target corneal AEs

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



US009446026B2

(12) **United States Patent**
Bingaman et al.

(10) **Patent No.: US 9,446,026 B2**
(45) **Date of Patent: Sep. 20, 2016**

(54) **OCULAR FORMULATIONS FOR DRUG-DELIVERY TO THE POSTERIOR SEGMENT OF THE EYE**

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(73) Assignee: **PanOptica, Inc.**, Bernardsville, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 20 days.

(21) Appl. No.: **14/211,427**

(22) Filed: **Mar. 14, 2014**

(65) **Prior Publication Data**

US 2014/0303219 A1 Oct. 9, 2014

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,891,913	A	4/1999	Sallmann
6,235,764	B1	5/2001	Larson et al.
2002/0151573	A1	10/2002	Gant
2005/0074497	A1	4/2005	Schultz
2007/0020336	A1	1/2007	Loftsson

FOREIGN PATENT DOCUMENTS

WO	WO 2013/126799	A1	8/2013

OTHER PUBLICATIONS

Fleisher, D. et al., "Improved oral drug delivery: solubility limitations overcome by the use of prodrugs", Advanced Drug Delivery Reviews, vol. 19, (1996), pp. 115-130.
Stella V. et al., "Cyclodextrins", Toxicologic Pathology, vol. 36, (2008), pp. 30-42.
Robinson R. et al., "Discovery of the Hemifumarate and (α-L-Alanyloxy)methyl Ether as Prodrugs of an Antirheumatic Oxindole: Prodrugs for the Enolic OH Group", J. Med. Chem., vol. 39, (1996), pp. 10-18.

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PanOptica is led by individuals with extensive ophthalmology research, development, and commercial experience

PanOptica Leadership

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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)

David Bingaman, DVM, ACVO, PhD

Head, Retina Dev.

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