Advances in Ocular Drug Delivery

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Disclosures - Walter O. Whitley, OD, MBA, FAAO has received consulting fees, honorarium or research funding from:

- Alcon
- Allergan
- Bausch and Lomb
- Biotissue
- Beaver-Visitec
- Carl Zeiss Meditec
- Glaukos
- J&J Vision
- Ocusoft
- Science Based Health
- Shire
- Sun Pharmaceuticals
- TearLab Corporation
- Tearscience

- Collaborative Eye – Co-Chief Medical Editor
- Review of Optometry – Contributing Editor

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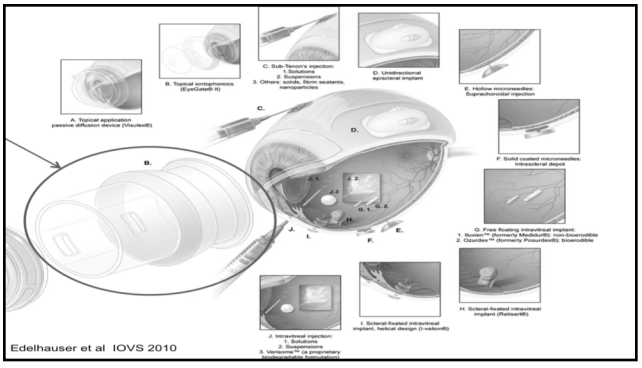
Current Drug Delivery

- Orals
- Eye Drops
- Transdermal
- Injections
- Others???

3



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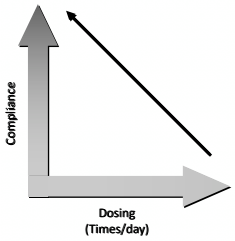
Patient Compliance and Dosing

- Literature review of 76 studies show
  - Compliance increases with decreased dosage regimen and complexity[1]
  - 79% compliance with QD regimen vs 51% for QID regimens (p=0.001)[1]
  - Simpler, less-frequent dosing results in better compliance in a variety of therapeutic classes[1]



1. Claxton et al. *Clinical Therapeutics.* 2001; 23:1296-1310.

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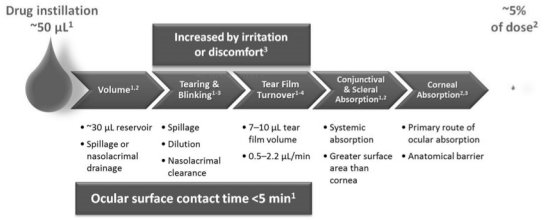
Topical Drug Delivery Considerations



1. Ghate D, Edelhauser HF. Ocular drug delivery. Expert Opin Drug Deliv. 2006;3(2):275-287. 2. Gaudana R, Ananthula HK, Parenky A, Mitra AK. Ocular drug delivery. AAPS J. 2010;12(3):348-360. 3. Coffey MJ, Decory HH, Lane SS. Development of a non-settling gel of 0.5% loteprednol etabonate for anti-inflammatory use as an ophthalmic drop. Manuscript in preparation. 4. McGhee CN. An overview of topical ophthalmic drugs and the therapeutics of ocular infection. http://www.fmhs.auckland.ac.nz/soph/ophthalvalley/teaching/_docs/optometry-355-05-pharmacokinetics.pdf. Accessed October 25, 2012. 5. Kaur IP, Kanwar M. Ocular preparations: the formulation approach. Drug Dev Ind Pharm. 2002;28(5):473-493.

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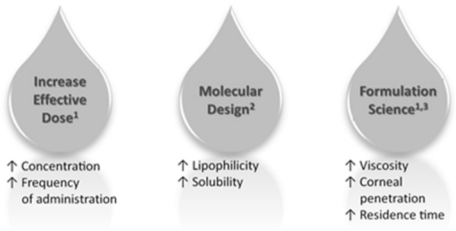
Strategies to Improve Topical Ocular Drug Delivery



1. Ghate D, Edelhauser HF. Expert Opin Drug Deliv. 2006;3(2):275-287. 2. Shirasaki Y. J Pharm Sci. 2008;97(7):2462-2496 3. Kaur IP, Kanwar M. Drug Dev Ind Pharm. 2002;28(5):473-493. 4. Barar J, et al. Expert Opin Drug Deliv. 2008;5(5):567-581

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Key Approaches to Improve Ocular Bioavailability

- Prodrug strategies
- Excipients
  - Cyclodextrins
- Penetration enhancers
- Dosage forms
  - Polymeric gels
  - Bioadhesive hydrogels
  - Temperature induced gelation
  - pH induced gelation
  - Osmotically induced gelation
  - Combination of polymers
- Microneedling
- Colloidal systems
  - Liposomes
  - Niosomes
  - Cubosomes
  - Microemulsions
  - Nanoemulsions
  - Nanoparticles

Achouri D., Alhanout, K., Piccerelle, P. Recent advances in ocular drug delivery. *Drug Development and Industrial Pharmacy.* 2012

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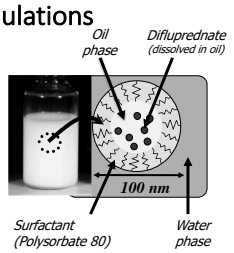
0.05% Emulsion Formulations

- Cyclosporine (Restasis) & Difluprednate (Durezol)
- Only 4 manufacturers with technology
- Excellent drop-to-drop dose uniformity compared to suspensions[1]
- More bioavailable than a suspension formulation of same drug[2]



1. Stringer W, Bryant R. Dose uniformity of topical corticosteroid preparations: difluprednate ophthalmic emulsion 0.05% vs. branded and generic prednisolone acetate ophthalmic suspension 1%. Clin Ophthalmol. 2010 Oct 5;4:1119-24.
2. Inoue, J., et al. Preclinical pharmacokinetics of difluprednate ophthalmic emulsion. Invest Ophthalmol Vis Sci. 2007;48:ARVO E-Abstract 2651.

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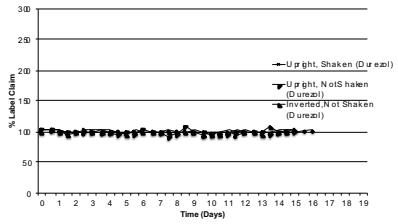
Dose Uniformity: Difluprednate Emulsion



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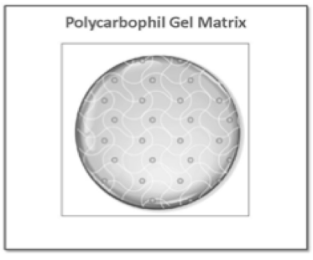
Mucoadhesive Technology

- Polycarbophil[1]
  - High molecular weight polymer
    - Not absorbed into ocular tissues
- Mucoadhesive
  - Binds to the mucin layer of biological membranes[1,2]
  - Polycarbophil is one of the most adherent mucoadhesives[3]
- Engineered to adhere to the ocular surface[4-6]



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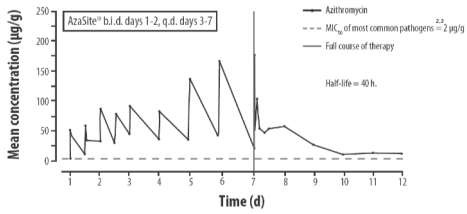
Multiple-Dose Rabbit: Azithromycin Conjunctiva Concentrations[1]



1. Data on file. Inspire Pharmaceuticals Inc, Study report 104U0207
2. Data on file. Inspire Pharmaceuticals Inc, NDA Study Report 01-401-003
3. Data on file. Inspire Pharmaceuticals Inc, NDA Study Report 01-401-004

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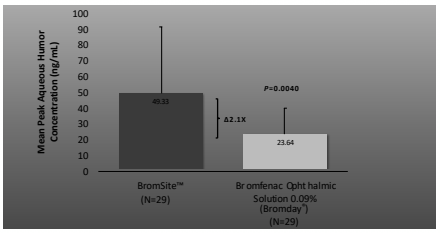
Use of DuraSite® Results in Increased Aqueous Humor Concentrations



US National Institutes of Health. Aqueous humor concentration of InSite Vision (ISV) 303 (bromfenac in DuraSite) to Bromday once daily (QD) prior to cataract surgery. https://clinicaltrials.gov.

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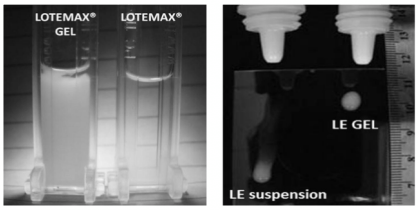
Mucoadhesive Adaptive Viscosity: Polycarbophil Gel Matrix



Gel at Rest; Viscous Liquid in the Eye

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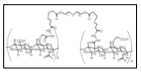
CMHA-S Crosslinked Hyaluronic Acid

- HA occurs naturally in the human body with qualities ideal for the ocular surface
  - Promotion of wound healing and lubrication
- Native HA has a relatively short half-life
- Crosslinking HA creates a 3D structure that stabilized the molecule
  - Adheres longer to the ocular surface (up to 90 min)
  - Higher viscosity that thins with blinking and is non blurring
  - Matrix protects the ocular surface



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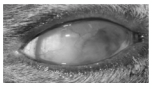
CMHA-s: Animal studies

- Commercially available as a veterinary device;
  - Manufactured by SentrX Animal Care
  - Sold in the U.S. by Bayer Animal Health as Remend® Corneal Repair[1]
  - Sold world wide with 5 years experience in thousands of dogs, cats and horses, with an excellent safety profile
- Efficacy has been demonstrated in masked, randomized clinical studies of corneal defects in dogs and cats

MOLLY A 12 YEAR OLD CAT WITH A NON-HEALING CORNEAL DEFECT AT 42 DAYS (A)

HEALING ULCER AFTER 12 DAYS WITH 0.75% CMHA-S GEL DROPS



1. EyeGate (NASDAQ: EYEG) has human ophthalmic rights only. Visit http://www.bayerdvm.com/show.aspx/remend-cross-linking-video

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CMHA-s: Ocular bandage Gel

- A clear hydrogel (or liquid-gel) eye drop with a 0.75% concentration of CMHA-S
  - Crosslinked to provide reduced degradation on the eye
  - Exhibits significant shear thinning properties
    - Enables better residence time with no optical blur
- Forms a thin layer over the ocular surface, protecting the eye
  - May accelerate re-epithelialization of corneal epithelial defects
    - PRK, superficial keratectomy, PKP
    - Corneal abrasions and ulcers
    - Neurotrophic keratitis
    - Severe SPK

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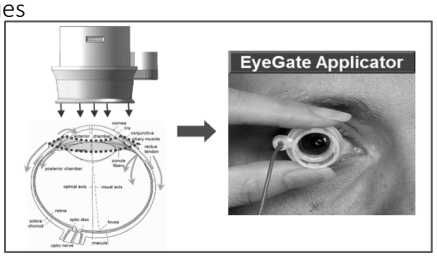
Iontophoresis Platform: A Non-Invasive Method of Propelling Charged Active Compounds Into Ocular Tissues



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Conclusions

- EGP-437 is safe and effective in reducing inflammation and preventing pain as early as Day 1 with 2 different iontophoretic doses.
- Best responses observed with 4.5 mA-min and 14.0 mA-min doses
- Percentage of patients with ACC count of zero greater than Durezol historical data at Day 7 and Day 28
- Percentage of patients with zero pain better than Durezol historical data at Day 4, 7, and 14
- Phase 2b trial initiation targeted for 1H 2017

EGP-437 effectively controls post operative pain and inflammation without the need for drop therapy

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Ophthalmic Delivery Systems

Versidoser

- Disposable/reloadable multi-dose ophthalmic delivery systems
  - VersiDoser – Liquid
  - VRx2 – Powers
- Packaged in unit dose blisters

https://magic-touch-eye.myshopify.com
http://www.mysticpharmaceuticals.com/test2/opthalmic.html

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Cataract Considerations

Issues with Cataract Post Op Drops

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TriMoxi or DexMoxi Intravitreal Injection

An injection of an antibiotic & steroid combination in the eye at the time of surgery.

Preparation:

1. triamcinolone or dexamethasone
2. moxifloxacin

→ One intravitreal injection

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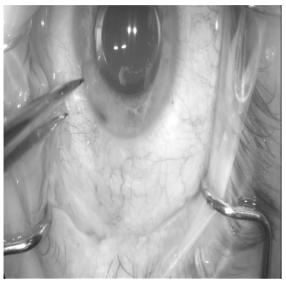
Pars plana injection into the vitreous cavity.

Medicine is injected after the IOL placement.

Patients are still under anesthesia so it is mostly painless



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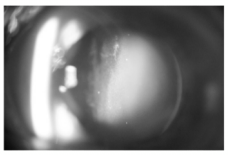
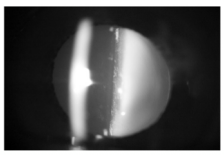
What Will the Doctor See???

View of the injected medication 2 hours after injection





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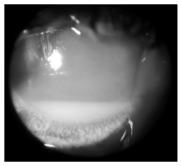
Benefits…

Compliance **Convenience** **Cost**



$$$$$

https://en.wikipedia.org/wiki/Endophthalmitis

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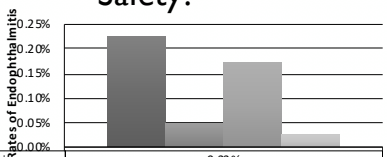
Safety?



A-no antibiotic	0.23%
B-intracameral cefuroxime	0.05%
C-topical levofloxacin	0.17%
D-intracameral & topical	0.03%

Braga-Mele, R., Chang, D., Henderson, B., Mamalis, N., Talley-Rostov, A., & Vasavada, A. (2014, December). Intracameral antibiotics: Safety, efficacy, and preparation. *Journal of Cataract & Refractive Surgery, 40*, 2134-2141.

5-fold decrease in endophthalmitis with intracameral cefuroxime

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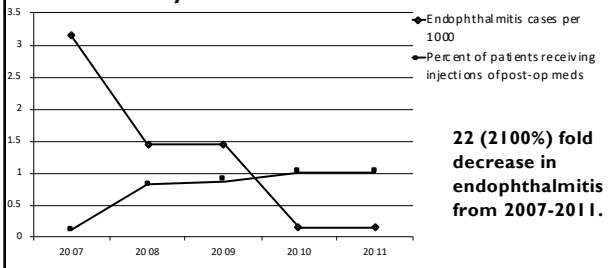
Kaiser Study



22 (2100%) fold decrease in endophthalmitis from 2007-2011.

Shorstein, N., Winthrop, K., & Herrinton, L. (2013, January). Decreased postoperative endophthalmitis rate after institution of intracameral antibiotics in a Northern California eye department. *Journal of Cataract & Refractive Surgery, 39*, 8-14.

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Concerns with Injections

1. Cystoid Macular Edema
   1. This study measured macular thickness in both arms at both 1 week and 1 month post-op
   2. No statistically significant difference in macular thickness

Clinical Ophthalmology

CLINICAL TRIAL REPORT

Transzonular vitreous injection vs a single drop compounded topical pharmaceutical regimen after cataract surgery

Fisher, B. L., & Potvin, R. (2016). Transzonular Vitreous Injection vs. a Single Drop Compounded Topical Pharmaceutical Regimen After Cataract Surgery. *Clinical Ophthalmology, 10*, 1297-1303.

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Concerns with Injections

- Cystoid Macular Edema
- Steroid response/ IOP spikes
  - Compared at Baseline, 1 day PO, 1 week PO, and 1 month PO
  - No statistically significant difference in IOP, no significant drift over time.


Clinical Ophthalmology

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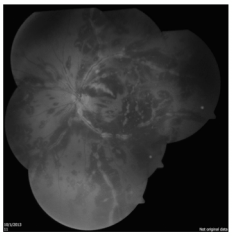
Concerns with Injections

1. Cystoid Macular Edema
2. Steroid response/ IOP spikes
3. HORV



Fisher, B. L., & Potvin, R. (2016). Transzonular Vitreous Injection vs. a Single Drop Compounded Topical Pharmaceutical Regimen After Cataract Surgery. *Clinical Ophthalmology, 10*, 1297-1303.

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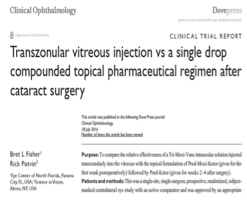
Concerns with Injections

1. Overall experience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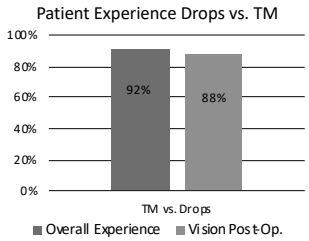

Fisher, B. L., & Potvin, R. (2016). Transzonular Vitreous Injection vs. a Single Drop Compounded Topical Pharmaceutical Regimen After Cataract Surgery. *Clinical Ophthalmology, 10*, 1297-1303.

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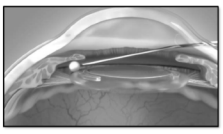
EYEPOINT PHARMACEUTICALS

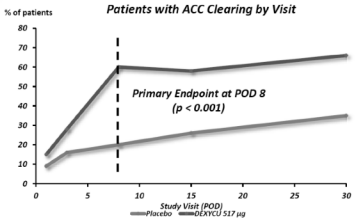
DEXYCU (dexamethasone intraocular suspension) 9%

FDA Approved February 9, 2018



Bioerodible Verisome® technology Administered as a single dose of 5-µL intraocularly into the posterior chamber, behind the iris, at the end of ocular surgery

Patients with ACC Clearing by Visit



Dexamethasone Intraocular Suspension 9%, (DEXYCU®), is a corticosteroid indicated for the treatment of postoperative inflammation.

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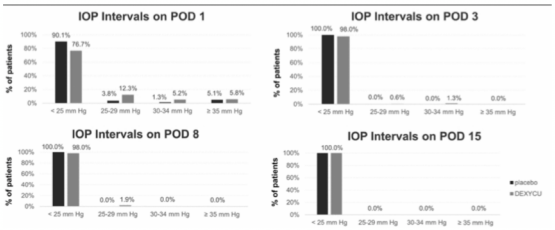
Dexycu



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Dextenza – Dexamethasone 0.4mg Insert

- FDA Approved 12/18 or post-surgical ocular inflammation and pain
  - Intracanalicular Plug
  - Drug released over 30 days
- DEXTENZA successfully met the trial's two primary efficacy endpoints, absence of ocular pain on day 8 and absence of ocular inflammation on day 14 when compared to placebo
- Other future considerations??

http://www.ocutx.com/pipeline/dexamethasone-punctum-plug

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DEXTENZA

Post-Surgical Ocular Pain

	Phase 2		Phase 3a		Phase 3b	
	DEXTENZA	Placebo	DEXTENZA	Placebo	DEXTENZA	Placebo
Absence of Pain at Day 8	79.3%	31.0%	76.1%	36.1%	77.5%	58.8%

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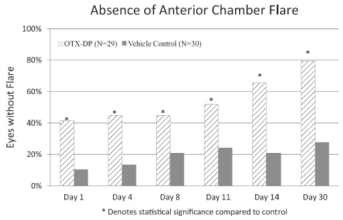
DEXTENZA



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LotemaxSM
(loteprednol etabonate 0.38% gel)

- Submicron particles have more surface area exposed to tears, driving **rapid drug dissolution**.
- **~2x greater penetration to the aqueous humor than LOTEMAX® GEL (loteprednol etabonate ophthalmic gel) 0.5%[2]**
- *Pooled analysis of Phase 3 clinical studies.
  - **Study 1:** 29%LOTEMAX® SM (N=171) vs 9% vehicle (N=172).
  - **Study 2:** 31%LOTEMAX® SM (N=200) vs 20% vehicle (N=199); *P*<0.05 for all.

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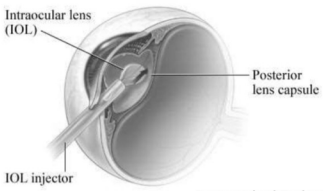
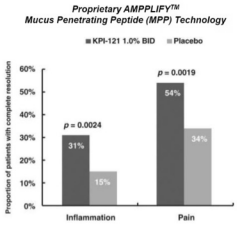
kala PHARMACEUTICALS

INVELTYS™ (loteprednol etabonate ophthalmic suspension) 1%

FDA Approved August 22, 2018





Loteprednol Etabonate Ophthalmic Suspension, 1% (INVELTYS®), is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.

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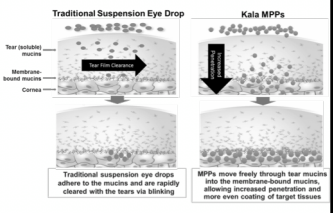
INVELTYS™ (KPI-121 1%)
Kala Pharmaceuticals

- A topical twice-a-day product candidate for the treatment of inflammation and pain in patients who have undergone ocular surgery.
- Utilizes Mucus Penetrating Particles (MMP) which binds to mucin in the eye and slowly release loteprednol etabonate



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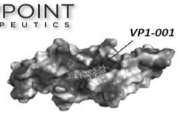
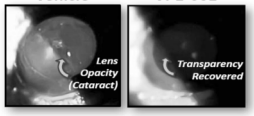
Cataract Prevention Drug?

VIEWPOINT THERAPEUTICS

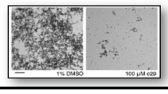
Sterols Target Crystallin to Restore Lens Transparency in Murine Cataract Models



VP1-001 binds and stabilizes the dimer of cryAB to reverse aggregation



Slit lamp biomicroscopic photographs from R120G cryAB mice dosed topically with VP1-001 eye drops



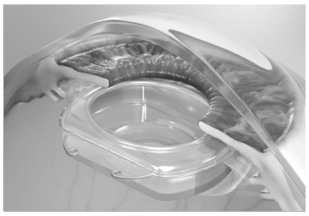
Activity confirmed in canine cataract model

www.viewpointtherapeutics.com

40

Gemini Refractive Capsule
Omega Ophthalmics

- Drug delivery
- Biometric sensors
- Lens technology



41

HARMONI Modular IOL System

- Base implanted in capsular bag
- OCT is done to establish exact position of the HARMONI base
- In the same setting, optic power is optimized based on concrete data from OCT imaging

42

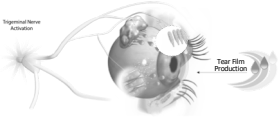
TRUETEAR™: PRODUCT INNOVATION

- First-ever neurostimulation device in eye care
- An easy-to-use and drug-free option to temporarily increase tear production during neurostimulation in adult patients
- Provides small electrical pulses to stimulate production of your own natural tears
- First "smart" device in eye care with *Bluetooth*® enabled and connected application

43

The Parasympathetic Nervous System (PNS) Is a Critical Regulator of the Lacrimal Functional Unit (LFU) and a Healthy Tear Film

The **parasympathetic nervous system** regulates the Lacrimal Functional Unit (LFU) and Tear Film Production via the Trigeminal Nerve **accessible within the nose**



[1] Gupta A, Heigle T, Pflugfelder SC. Nasolacrimal stimulation of aqueous tear production. *Cornea*. 1997 Nov;16(6):645–8.
[2] van der Werf, F. R. A. N. S., Baljet, B., Prins, M. A. A. R. T. E. N., & Otto, J. A. (1996). Innervation of the lacrimal gland in the cynomolgous monkey: a retrograde tracing study. *Journal of anatomy*, 188(Pt 3), 591.
[3] LeDoux, M. S., Zhou, Q., Murphy, R. B., Greene, M. L., & Ryan, P. (2001). Parasympathetic innervation of the meibomian glands in rats. *Investigative ophthalmology & visual science*, 42(11), 2434-2441.
[4] Dartt, D. A., Mccarthy, D. M., Mercer, H. J., Kessler, T. L., Chung, E. H., & Zieske, J. D. (1995). Localization of nerves adjacent to goblet cells in rat conjunctiva. *Current eye research*, 14(11), 993-1000.

44

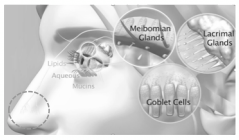
Disruptive Approach to Treating Dry Eye Disease Based on Neuroscience and Role of the LFU

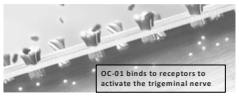
Ideal Compound → **Novel Mechanism of Action**

The trigeminal nerve is **accessible within the nasal cavity** and can be activated by stimulating **Nicotinic acetylcholine receptors** (nAChR)

OC-01 **nAChR Agonist with Unique Receptor Activation Profile**

- Nasal Spray Solution
- Multi Dose Preservative Free
- 50µl volume (Standard is 120µl)
- BID Dosing
- 30 Day Supply





45

OTX-101 – Sun Pharmaceuticals

- A nanomicellar formulation of cyclosporine 0.09%
- In this 12 week, multicenter, randomized, double-masked, vehicle controlled Phase 3 confirmatory study, 744 dry eye patients were treated either with OTX-101 or its vehicle.
  - Met primary endpoint of Schrimer's Score ($p<0.0001$)
  - The demonstration of efficacy at 12 weeks is earlier than other drugs approved for dry eye in the same class.

46

NovaTears / EvoTears

- Innovative mode of action due to the patented EyeSol®-Technology – Made in Germany
- Forms a protective layer over the tear film
- Long-lasting effect for greater patient satisfaction – clinically proven[1]
- Extremely well tolerated as free from preservatives, phosphates and emulsifiers

47

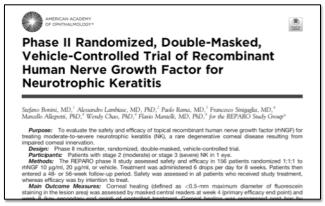
Neuropathic Dry Eye Pain

- Role of cannabis
- EyeSol, Novaliq – a novel semi-fluorinated alkane drug delivery technology
  - Low surface tension
  - No water
  - Metabolically inert
  - Refractive index similar to H20

Steven, P. Realm of dry eye therapy expanding. Ophthalmology Times. November 15, 2017.

48

OXERVATE™ (cenegermin-bkbj 20 mcg/ml) was approved by FDA in August 2018



Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis

Stefano Bonini, MD,[1] Alessandro Lambiase, MD, PhD,[1] Paolo Rama, MD,[2] Francesco Sinagaglia, MD,[3] Marcello Allegretti, PhD,[3] Wendy Chao, PhD,[3] Flavio Mantelli, MD, PhD,[3] *for the REPARO Study Group*[4]

Purpose: To evaluate the safety and efficacy of topical recombinant human nerve growth factor (rhNGF) for treatment of moderate-to-severe neurotrophic keratitis (NK), a rare degenerative corneal disease resulting from impaired corneal innervation.
Design: Phase II multicenter, randomized, double-masked, vehicle-controlled trial.
Participants: Patients with stage 2 (moderate) or stage 3 (severe) NK in 1 eye.
Methods: The REPARO phase II study assessed safety and efficacy in 156 patients randomized 1:1:1 to rhNGF 10 μg/ml, 20 μg/ml, or vehicle. Treatment was administered 6 drops per day for 8 weeks. Patients then entered a 48- or 56-week follow-up period. Safety was assessed in all patients who received study treatment, whereas efficacy was by intention to treat.
Main Outcome Measures: Corneal healing (defined as <0.5-mm maximum diameter of fluorescein staining in the lesion area) was assessed by masked central readers at week 4 (primary efficacy end point) and

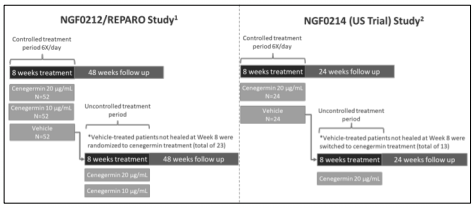
- Approved for the treatment of neurotrophic keratitis in adults and children age 2 and older
- Available for ordering since January 2019
- Developed by Dompé pharmaceuticals, available through specialty pharmacy

Bonini S, Lambiase A, Rama P *et al.* Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. *Ophthalmology* 2018;125:1332-1343.

49

OXERVATE™ (cenegermin-bkbj) 0.002%

Pivotal Trials Study Design: All subjects with Stage 2 or 3 NK

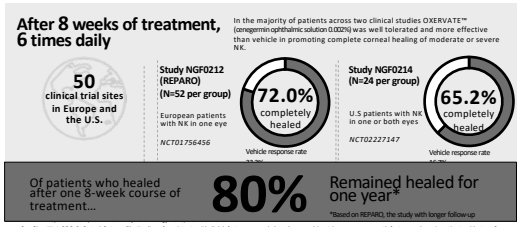


*****The primary efficacy endpoint, which was determined by a central reading center, was "complete corneal healing" defined as 0 mm staining in the lesion area and no persistent staining in the rest of the cornea**

1. Bonini S, Lambiase A, Rama P *et al.* Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. *Ophthalmology* 2018;125:1332-1343.
2. Chao W, J. BDC, R. D *et al.* Data on file. Healing of persistent epithelial defects or corneal ulcers by recombinant human nerve growth factor eye drops in patients with stage 2 or 3 neurotrophic keratitis. Presented at: Congress of the European Society of Ophthalmology (SOE) 10–13 June, 2017, Barcelona, Spain. 2017.

50

Up to 72% of patients achieved complete corneal healing; 80% of healed patients were recurrence free after 1 year*



2. Chao W, J. BDC, R. D *et al.* Data on file. Healing of persistent epithelial defects or corneal ulcers by recombinant human nerve growth factor eye drops in patients with stage 2 or 3 neurotrophic keratitis. Presented at: Congress of the European Society of Ophthalmology (SOE) 10–13 June, 2017, Barcelona, Spain. 2017.

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Glaucoma Considerations

- When COMPLIANCE with drops is low
- When MEDICAL THERAPY FAILS
- When the PROGRESSION continues to WORSEN
- Treatment options
  - More medications
  - Laser therapy
  - Surgical intervention

52

Ocular Science Glaucoma Drops

TIMOLOL AND LATANOPROST
A fixed-combination solution dosed daily (at your physician's instruction) for the reduction of intraocular pressure

$25.00/ 1 month supply

TIMOLOL, BRIMONIDINE AND DORZOLAMIDE (AM FORMULA)
A fixed-combination solution for the reduction of intraocular pressure. This drop is dosed twice daily or, if used in conjunction with an evening dose of our PM formula, it can be dosed daily in the morning.

$30.00/ 1 month Supply

TIMOLOL, BRIMONIDINE, DORZOLAMIDE AND LATANOPROST (PM FORMULA)
A fixed-combination for the reduction of intraocular pressure. It is typically dosed in the evening, in conjunction with a morning dose of our AM formula.

$35.00/ 1 month supply

- 180 day shelf life
- 0.02% BAK preservative
- Ships directly to patient

53

Recent and Future Additions to our Glaucoma Drop Armamentarium

- Latanoprostene bunod (Bausch + Lomb) – Nitric oxide donating prostaglandin analog
  - Increases both uveoscleral and trabecular outflow
- Rhopressa (Aerie) – Inhibition of Rho kinase and of norepinephrine transporter
  - Increases trabecular outflow
  - Reduces aqueous production
  - Decreases episcleral venous pressure
- Roclatan (Aerie) – Combined mechanisms of Rhopressa and latanoprost

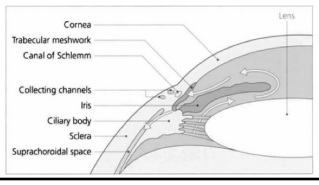
54

Schlemm's Canal	Type
Stents	
	iStent
	iStent Inject
	Hydrus
Dilation	
	Visco 360
	ABiC
Cutting	
	Kahook Dual Blade
	OMNI/GATT
Ablation	
	Trabectome

Suprachoroidal	Type
Stents	
	*Cypass
	*iStent Supra

Subconjunctival	Type
Stents	
	Xen
	InnFocus Micro

Cilioablative	Type
External	
	Micropulse
Internal	
	ECP



55

MIGS ADVANTAGES

Safer

Avoids serious complications

No Bleb

Gentler

Faster recovery

Less OR time

Less glaucoma meds

Reduction of IOP

Decreased IOP fluctuations

Combined with cataract sx

Spares the conjunctiva

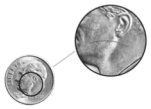
Good for contact lens wearers

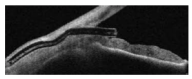
Fewer follow-up appointments

56

The XEN® Gel Stent

- A glaucoma implant designed to reduce intraocular pressure in eyes suffering from refractory glaucoma[1]
- 6-mm length, 45-micron inner diameter—about the length of an eyelash[1,2]
- Composed of gelatin, cross-linked with glutaraldehyde[1]





1. XEN® Directions for Use; 2. Vogt et al. In: Blume-Peytavi et al, eds. *Hair Growth and Disorders*. 2008.

57

Xen 45 Gel Stent: US Pivotal Clinical Trial

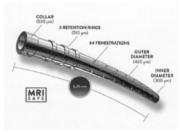
	Baseline	12 month
Medicated IOP	25.1 (3.7)	15.9 (5.2)
Glaucoma Meds	3.5 (1.0)	1.7 (1.5)

76.3% of patients reported a mean diurnal IOP reduction of ≥ 20% from medicated baseline at 12 months

58

CyPass Withdrawal

- Early September 2018, CyPass withdrawn
- COMPASS-XT – 5 year extension of original trial
  - Significant ECL (>30%) statistically higher in CyPass (27.2%) vs. Phaco alone (10%)
  - Positioning of stent correlated to ECL rate
    - Retention rings visible
    - Angulation



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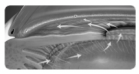
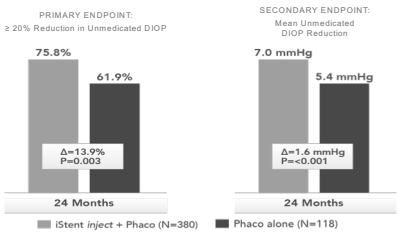
iStent *inject* Surgical Procedure

- Placed in the eye during cataract surgery – after phaco
- The procedure is straightforward, astigmatically-neutral, and minimally traumatic to the eye
- iStent *inject* has an overall safety profile similar to cataract surgery
  - Early complications same as iStent -- IOP spike, hyphema, PAS at stent lumen
- Reduces the risk of hypotony by utilizing the natural episcleral venous pressure



60

iStent *inject* PIVOTAL TRIAL
Proven Efficacy[1]



1. iStent inject® Trabecular Micro-Bypass System: Directions for Use, Part # 45-0176.

61

HORIZON Trial

	Stent + Cataract (n=369)	Cataract Only (n=187)
Baseline IOP (mm Hg) after washout	25.5 (+/- 3.0)	25.4 (+/-2.9)
24 months IOP (mm Hg) after washout	17.4 (+/-3.7)	19.2 (+/-3.8)
Unmedicated at 24 months	52.6%	54%
1 preoperative med	47.4%	46%
2 to 4 preoperative med		

Hydrus Microstent

62

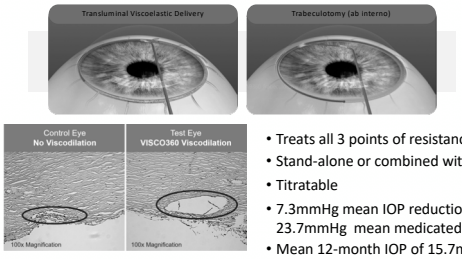
ABiC Efficacy[1]

- Combined cohort (n = 228)
- Average IOP reduction 30%, average reduction in medication use 50% at 12 months
  - ABiC + phaco (n = 130) – 23% IOP reduction, 50% fewer medications
  - Standalone (n = 98) – 37% IOP reduction, 67% fewer medications
- Results similar to previous canaloplasty studies

1. Ellex Science. Ab-Interno Canaloplasty – The Minimally Invasive Glaucoma Surgery That Keeps Its Promise. White Paper. 2016. https://www.ellex.com/uploads/Resources/Files/Ellex-ABiC-Whitepaper-12-Months.pdf

63

OMNI Surgical System (Sight Sciences)



- Treats all 3 points of resistance
- Stand-alone or combined with CE
- Titratable
- 7.3mmHg mean IOP reduction from 23.7mmHg mean medicated baseline
- Mean 12-month IOP of 15.7mmHg.

64

And There's More

- Canaloplasty
- Glaukos Istent Supra
- Glaukos Istent Inject
- Allergan Bimatoprost SR
- Ocular Therapeutix SR Travaprost

Solx Gold Shunt

Kahook Dual Blade

65

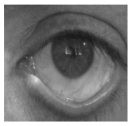
Drug Eluding Punctal Plugs

Ocular Therapeutix

- Sustained-release travoprost in an intracanalicular depot composed of polyethylene glycol hydrogel and drug-containing microparticles
  - Drug elutes over 90 day period
  - In Phase 3 Clinical Trials

Mati Therapeutics

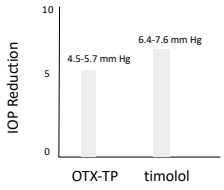
- Two formulations have been taken into clinical trials
  - Latanoprost for glaucoma
  - Olopatadine for allergy relief



66

Travoprost Punctum Plug

(OTX-TP, Ocular Therapeutix)



No hyperemia in OTX-TP

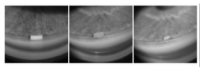
Retention Rates
91, 88, 48% @ days
60, 75, 90

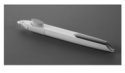
Ocular Therapeutix, Inc. Ocular Therapeutix TM reports on topline results of phase 2b glaucoma clinical trial. Press Release. 22 October 2016. http://investors.ocutx.com/phoenix.zhtml?c=253650&p=irol-newsArti- cle&ID=2100516. [Accessed 6 September 2016]

67

Bimatoprost Sustained Release Implant

- 7/17/19 FDA Accepts Allergan's New Drug Application for Bimatoprost Sustained-Release in Patients with Open-Angle Glaucoma or Ocular Hypertension
  - Based on two Phase III clinical trials
  - 1,122 Subjects





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24 Month Phase I/II Clinical Trial

bimatoprost pellet
(6, 10, 15, or 20 micrograms)

4 months – IOP reduction
7.2, 7.4, 8.1, 9.5 mm Hg
92% of patients

topical bimatoprost 0.03%

4 months – IOP reduction
of 8.4 mm Hg

Sustained at 6 mos. in 71%

69

Envisia - Travoprost SR Implant

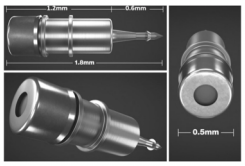
- ENV515 is engineered as a proprietary, fully biodegradable PRINT® (Particle Replication In Non-Wetting Templates) travoprost formulation that could offer sustained reduction in IOP for more than six months after a single dose
- Met Phase 2a primary efficacy endpoint
  - Change in diurnal IOP at Day 25
  - 28-Day dose – Decrease 28%

70

Travoprost Intraocular Implant

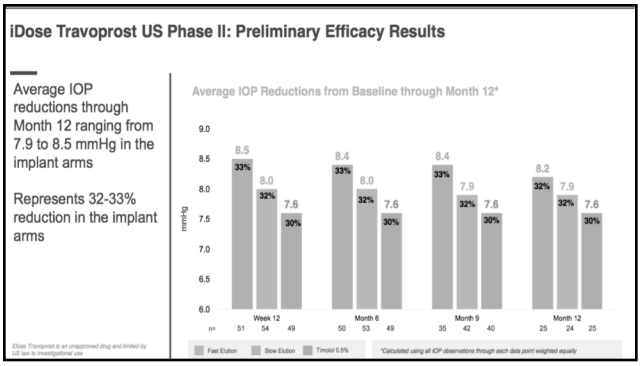
(iDose, Glaukos)

Resides in AC angle, anchored behind TM



- Length: 1.8 mm
- Diameter: 0.5 mm
- Titanium
- Non-ferrous

71



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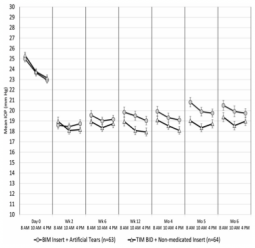
Bimatoprost Ring

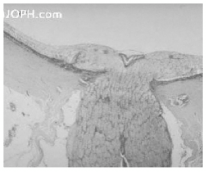
Retention Rate – 89%



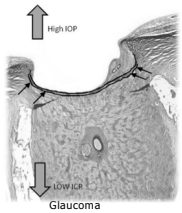
Brandt J, Sall K, DuBiner H, et al. Six-month intraocular pressure reduction with a topical bimatoprost ocular insert. *Ophthalmology*. 2016;123(8):1685-1694.

73

ICP effects the Nerve



Pseudotumor



Glaucoma

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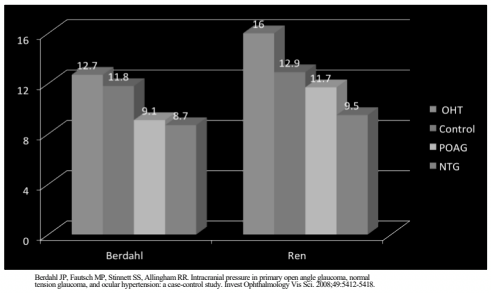
CSF Pressure in Glaucoma



Berdahl JP, Fautsch MP, Stinnett SS, Allingham RR. Intracranial pressure in primary open angle glaucoma, normal tension glaucoma, and ocular hypertension: a case-control study. Invest Ophthalmology Vis Sci. 2008;49:5412-5418.

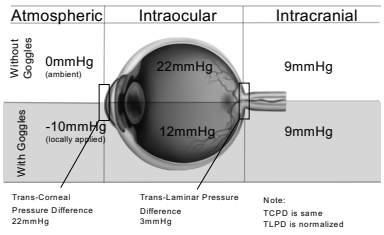
Ren R, Jonas JB, Tian G, et al. Cerebrospinal fluid pressure in glaucoma: a prospective study. Ophthalmology. 2010;117:259-266.

75

Balance Goggles

76

Treatment in Glaucoma



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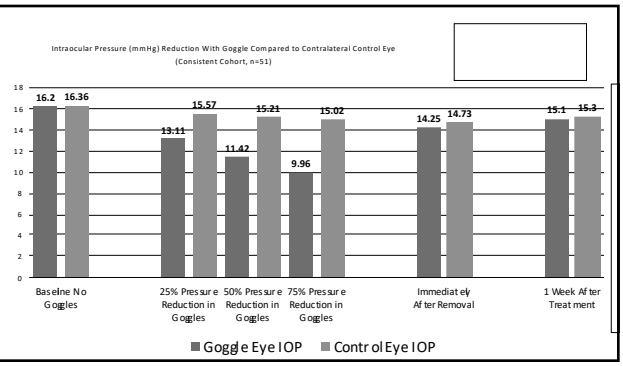

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Latanoprost-Eluting Contact Lens

Attractive option secondary to large residence time in the eye.

79

Latanoprost-Eluting Contact Lens

Comfort of Lens

Patient Compliance

Vision with Lens

Dry Eye/Ocular Surface Disease

Replacement Schedule

80

Preclinical Trial and Results

CL_{HI} (149g latanoprost) CL_{LO} (97g latanoprost)

VS

Topical latanoprost

~ 1 week

Ciolino JB, Ross AE, Tulsan R, et al. Latanoprost-eluting contact lenses in glaucomatous monkeys. Ophthalmology 2016; 123:2085 – 2092.

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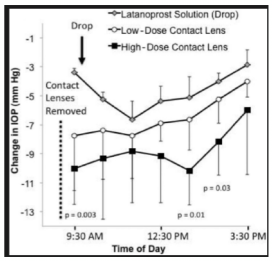
Preclinical Trial and Results



Ciolino JB, Ross AE, Tulsan R, et al. Latanoprost-eluting contact lenses in glaucomatous monkeys. Ophthalmology 2016; 123:2085 – 2092.

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CL Drug Delivery - Advantages

- Over 50% of the drugs released from a CL can diffuse into the cornea, which is at least 35 times more efficient than eye drops
- Ability to deliver drugs over extended time periods

i CC, Chauhan A (2006) Modeling ophthalmic drug delivery by soaked contact lenses. Ind Eng Chem Res 45: 3718-3734.

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CL Drug Delivery - Barriers

- Still no commercial products available since 1960s
- Silicon hydrogel CL addressed hypoxia-related complications
- Rapid release kinetics
  - May differ based on CL material / drug combos
  - Rate of drug release is not constant over time

i CC, Chauhan A (2006) Modeling ophthalmic drug delivery by soaked contact lenses. Ind Eng Chem Res 45: 3718-3734.

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CL Drug Delivery – What does the future hold?

- Molecular imprinting - Creates specific drug recognition sites within the polymer through the use of molecular templates
- Vitamin E coatings - Form diffusion barriers within the lens, which forces the target drug to take long complex paths to diffuse from the lens
- Nanoparticles - Encapsulated with the target drug can be loaded and released from the CL, and the extended release is controlled by the degradation of the nanoparticles
- Concerns - Frequent lens application?? Non-CL wearers?? Cost??

J CC, Chauhan A (2006) Modeling ophthalmic drug delivery by soaked contact lenses. Ind Eng Chem Res 45: 3718-3734.

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Conclusion

- Opportunity to address compliance issues
- Opportunity to improve efficacy while maintaining safety profile
- Numerous drugs in the pipeline so be ready to practice at the highest level of our great profession!!

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