

# Are Eye Drops Dead?

## *The Future of Ophthalmic Drug Delivery*



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Tschannen Eye Institute

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Tel Aviv, Israel  
14 February 2020

# Financial Disclosures



- **Allergan**
  - Consulting
    - Proposed PI of planned Phase 3 clinical trial of the bimatoprost sustained-release ring insert
  - Forsight Vision5 Laboratories (acquired by Allergan in 2016)
    - Research Support
      - PI of Phase 2 clinical trial of the bimatoprost sustained-release ring insert
    - Travel support
- **Aerie Pharmaceuticals**
  - Consulting
- **Carl Zeiss Meditec**
  - Consulting
- **Glaukos**
  - Stockholder
  - Former Advisory Board Member
- **Graybug Vision**
  - Consulting
- **InnFocus (acquired by Santen in 2016)**
  - Research Support, Phase 3 clinical trial - Site co-investigator
- **Laboratoires Théa**
  - Consulting
- **National Eye Institute**
  - PI of UC Davis Clinical Center for the Ocular Hypertension Treatment Study (OHTS) 20 year follow-up study

# The Treatment Paradox



Highly effective treatments for glaucoma and ocular hypertension exist...

- Prostaglandin Analogues (PGAs) Reduce the Likelihood of Progression by 34 - 42% / year<sup>1</sup>
  - Approved by FDA in 1990s; Excellent Safety Profile
- PGAs are widely used as 1<sup>st</sup> line treatment<sup>2</sup>

<sup>1</sup> NICE Guidelines: <http://www.nice.org.uk/nicemedia/live/12145/43888/43888.pdf>; Appendix F, p.246

<sup>2</sup> Calculated as follows: IMS data shows 14.25MM Rx's in 2012 for PGAs in USA. Mean medication possession ratio = 0.64 (Friedman *et al.*, *Invest Ophthalmol Vis Sci* 2007;48:5052–5057).  $((14.25\text{MM})/12 \text{ months})/0.64 \text{ Rx/Pt/Month} = 1.9\text{MM}$  patients

# Non-Adherence in Glaucoma



...but our patients don't take their drops

- Non-adherent glaucoma patients represent a large unmet need: >50%\* of patients
- Physicians are notoriously poor at identifying poorly-adherent patients†

\* Newman-Casey *et al.*  
Patterns of glaucoma medication adherence over four years of follow-up  
*Ophthalmology* 2015;122:2010-2021

\* Nordstrom *et al.*  
Persistence and adherence with topical glaucoma therapy  
*Am J Ophthalmol* 2005;140:598-606;

† Kass MA, Gordon M, Meltzer DW  
Can ophthalmologists correctly identify patients defaulting from pilocarpine therapy?  
*Am J Ophthalmol* 1986;101(5):524-30

# Non-Adherence in Glaucoma



Sustained release (SR) delivery of glaucoma medications may help address this challenge

# Why Sustained Release (SR)?



SR has the potential to provide long-term IOP lowering *without the need for daily dosing*

# Why Sustained Release?



- May reduce several barriers to treatment adherence
  - Struggling to get drops into the eye

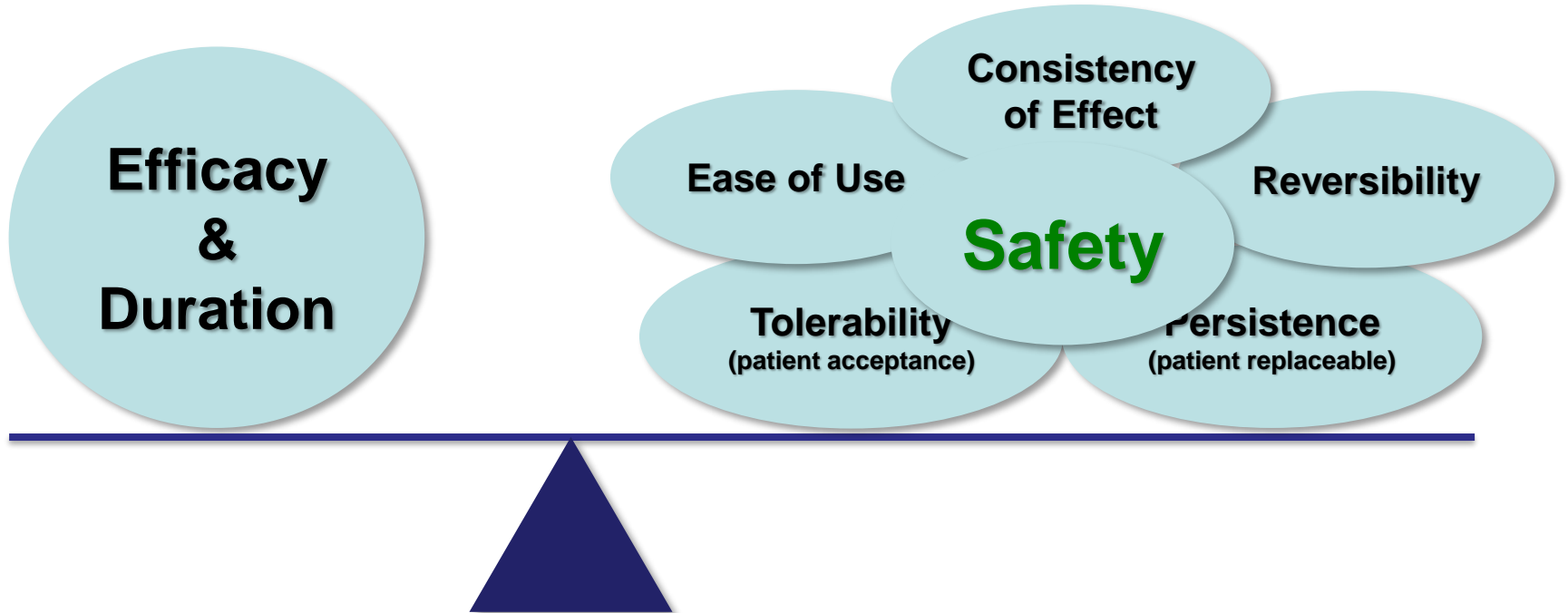
# Why Sustained Release?



- **May reduce several barriers to treatment adherence**
  - Struggling to get drops into the eye
  - Remembering multiple daily doses
  - **Adverse effects caused by preservative exposure to ocular surface or surrounding tissues**



# The SR Balancing Act



# The SR Balancing Act



- Glaucoma is a slowly-progressive disease
  - For early disease (and ocular hypertension), ***safety must be the highest priority***
    - In the OHTS the NNT (number needed to treat) was **20**

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    - **What is an acceptable NNH (number needed to harm)?**

# The SR Balancing Act



- Glaucoma is a slowly-progressive disease
  - For *early* disease (and ocular hypertension), *safety must be the highest priority*
    - In the OHTS the NNT (number needed to treat) was 20
    - What is an acceptable NNH (number needed to harm)?
  - For *advanced* disease, a modest safety penalty may be acceptable to achieve higher efficacy & duration of action

# The SR Glaucoma Pipeline\*



## Implantable

### Subconjunctival

- Erodeable drug pellets
- Drug-containing microspheres
- Mechanical reservoir (device)

### Intraocular

- Intravitreal
- Suprachoroidal
- Intracameral (erodeable & device)

## External

### Cornea

- Contact lens

### Punctal

- Drug-eluting punctal plug

### Conjunctival (cul-de-sac)

- Drug-eluting ring
- Microsphere-containing polymer gel

\* Based on publicly-available information as of late 2019

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Product (Company)	Description	Development Stage	Targeted Duration
Bimatoprost SR (Allergan)	Biodegradable Implant (anterior chamber)	NDA Submitted 7/17/2019	6 months
iDose (Glaukos)	Non-degradable Implant (anterior chamber)	Phase I/II	6 – 12 months
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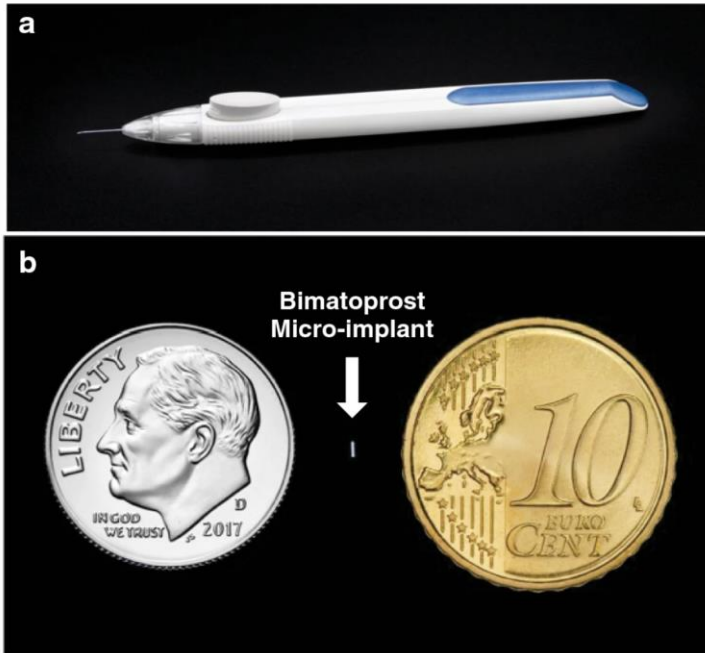
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# Bimatoprost SR



Bimatoprost sustained-release (SR) single-use implant applicator (a) and photograph of implant next to a dime and Euro for size comparison (b)

Drugs  
<https://doi.org/10.1007/s40265-019-01248-0>

ORIGINAL RESEARCH ARTICLE



## 24-Month Phase I/II Clinical Trial of Bimatoprost Sustained-Release Implant (Bimatoprost SR) in Glaucoma Patients

E. Randy Craven<sup>1</sup> · Thomas Walters<sup>2</sup> · William C. Christie<sup>3</sup> · Douglas G. Day<sup>4</sup> · Richard A. Lewis<sup>5</sup> · Margot L. Goodkin<sup>6</sup> · Michelle Chen<sup>6</sup> · Veronica Wangsadipura<sup>6</sup> · Michael R. Robinson<sup>6</sup> · Marina Bejanian<sup>6</sup> · for the Bimatoprost SR Study Group

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### Abstract

**Objective** The objective of this study was to evaluate the safety and intraocular pressure (IOP)-lowering effects over 24 months of biodegradable bimatoprost sustained-release implant (Bimatoprost SR) administration versus topical bimatoprost 0.03% in patients with open-angle glaucoma (OAG).

**Methods** This was a phase I/II, prospective, 24-month, dose-ranging, paired-eye controlled clinical trial. At baseline following washout, adult patients with OAG ( $N=75$ ) received Bimatoprost SR (6, 10, 15, or 20  $\mu\text{g}$ ) intracamerally in the study eye; the fellow eye received topical bimatoprost 0.03% once daily. Rescue topical IOP-lowering medication or single repeat administration with implant was permitted. The primary endpoint was IOP change from baseline. Safety measures included adverse events (AEs).

**Results** At month 24, mean IOP reduction from baseline was 7.5, 7.3, 7.3, and 8.9 mmHg in eyes treated with Bimatoprost SR 6, 10, 15, and 20  $\mu\text{g}$ , respectively, versus 8.2 mmHg in pooled fellow eyes; 68, 40, and 28% of pooled study eyes had not been rescued/retreated at months 6, 12, and 24, respectively. AEs in study eyes that occurred  $\leq 2$  days post-procedure typically were transient. After 2 days post-procedure, overall AE incidence was similar between study and fellow eyes, with some events typically associated with topical prostaglandin analogs having lower incidence in study eyes.

**Conclusions** Bimatoprost SR showed favorable efficacy and safety profiles up to 24 months, with all evaluated dose strengths demonstrating overall IOP-reducing effects comparable to those of topical bimatoprost. Targeted and sustained delivery of bimatoprost resulted in protracted IOP lowering, suggesting that Bimatoprost SR may represent a transformational new approach to glaucoma therapy. Clinicaltrials.gov identifier: NCT01157364

# Bimatoprost sustained-release pellet

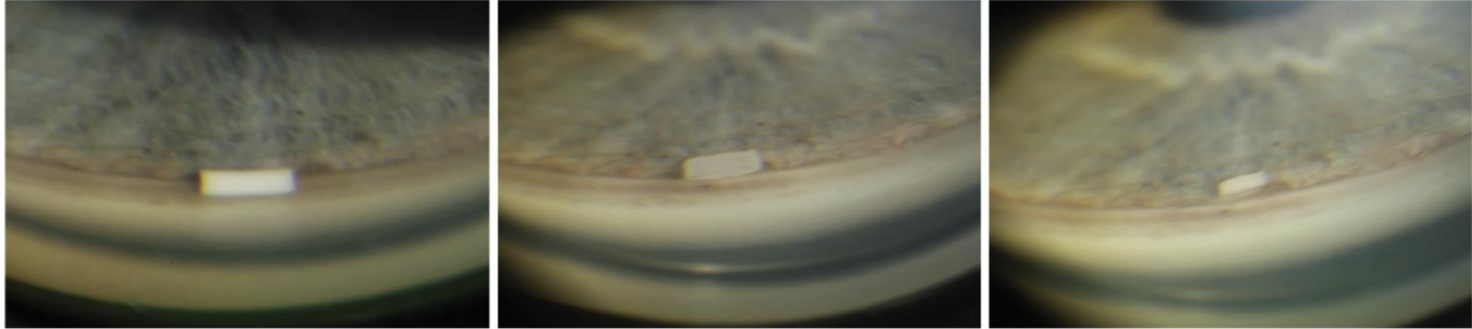


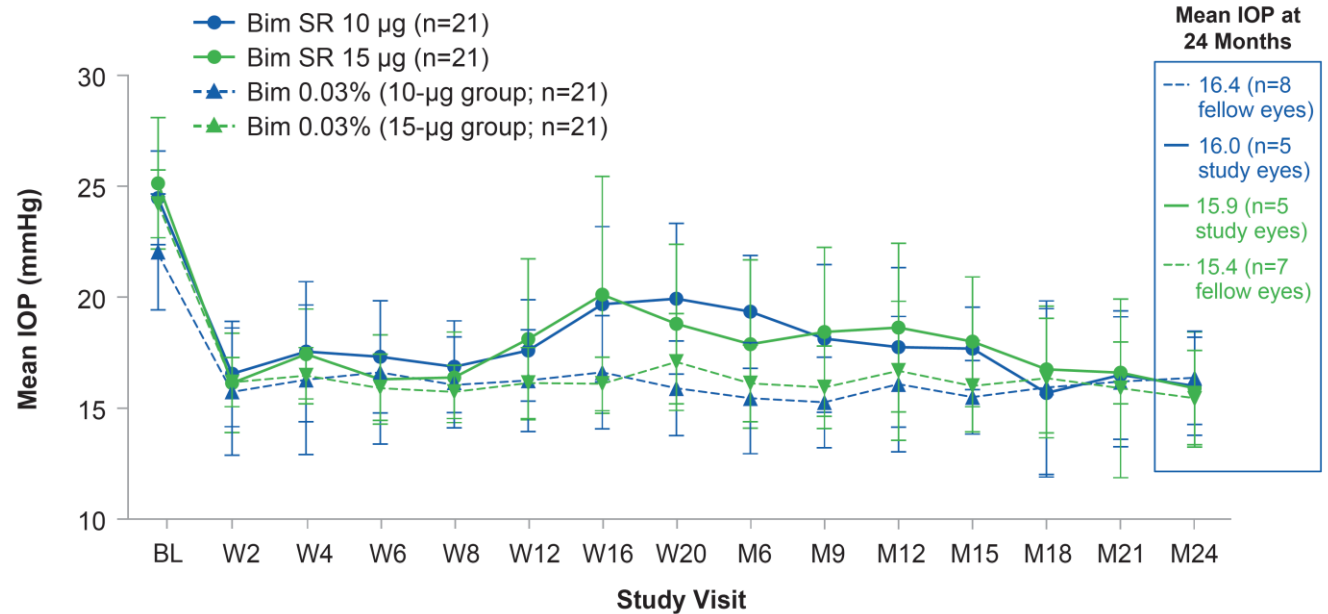
FIGURE 3. Gonioscopic photographs of bimatoprost sustained-release implant 10  $\mu$ g in the anterior chamber of an eye of a representative patient diagnosed with open-angle glaucoma at (Left) 2 weeks, (Center) 9 months, and (Right) 12 months after injection.

Lewis RA, Christie WC, Day DG *et al.*  
Bimatoprost Sustained-Release Implants for Glaucoma Therapy:  
6-Month Results from a Phase I/II Clinical Trial  
*Am J Ophthalmol* 2017;175(3):137-147

# Bimatoprost SR – 24 month data



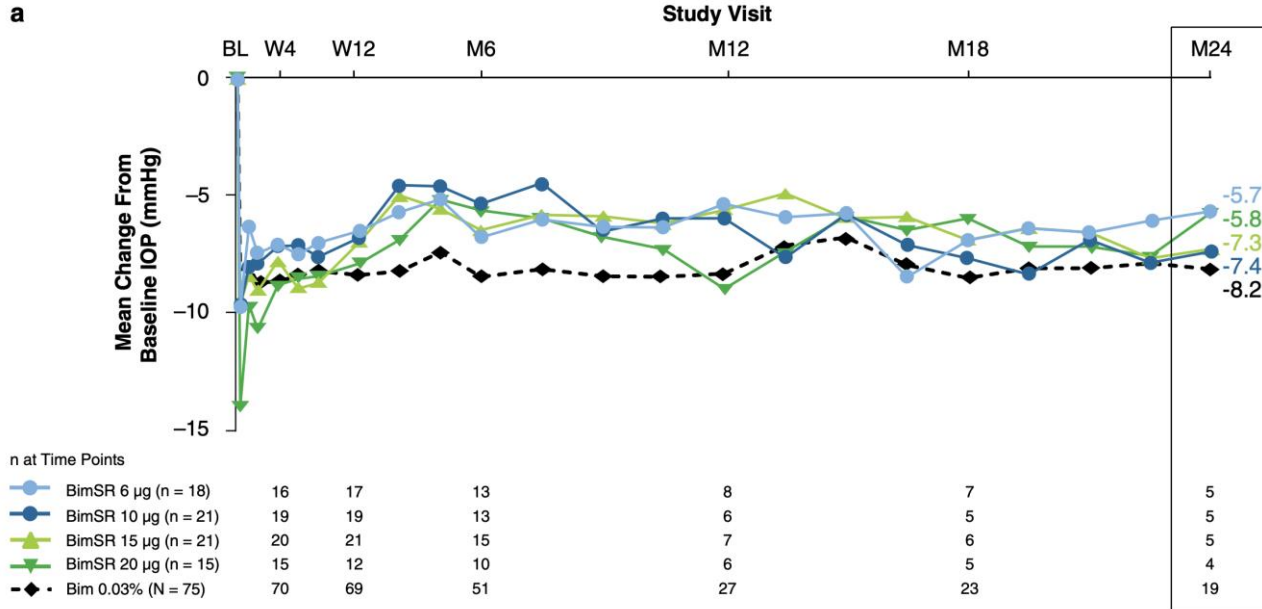
Mean IOP in Patients Receiving the Bim SR 10- or 15- $\mu$ g Dose Strengths **Without Rescue or Retreatment\***



Craven ER, Coote M, Walters T *et al.*  
Bimatoprost Sustained-Release Implant for Lowering Intraocular Pressure: Long-term Efficacy and Patient-Reported Outcomes.  
World Glaucoma Congress, March 2019  
Melbourne, Australia. Poster P-WT-138

\*Analysis based on observed values with data censored at rescue or retreatment

# Bimatoprost SR – 24 month data



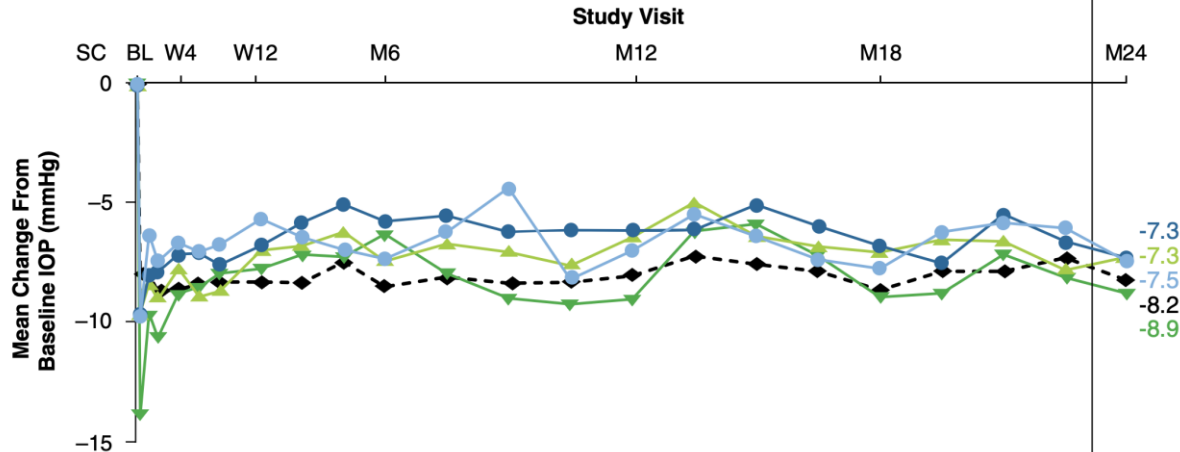
# Bimatoprost SR – 24 month data



**b**

Mean Meds=

BimSR 6 µg	1.22	0	0.18	0.17	0.24	0.56	0.65	0.64
BimSR 10 µg	1.14	0	0	0	0.37	0.68	0.83	0.75
BimSR 15 µg	1.19	0	0	0	0.43	0.72	0.67	0.67
BimSR 20 µg	1.53	0	0	0.20	0.67	0.85	1.38	0.90
Bim 0.03%	1.25	0	0	0.05	0.01	0.03	0.18	0.05



n at Time Points

● BimSR 6 µg (n = 18)	17	18	17	16	17	14
● BimSR 10 µg (n = 21)	19	19	19	19	18	16
▲ BimSR 15 µg (n = 21)	20	21	21	18	18	15
▼ BimSR 20 µg (n = 15)	15	15	15	13	13	10
◆ Bim 0.03% (N = 75)	71	73	72	66	66	55

Craven ER, Walters T, Christie WC *et al.*  
 24-Month Phase I/II Clinical Trial of Bimatoprost Sustained-Release Implant (Bimatoprost SR) in Glaucoma Patients  
*Drugs* 2019; ePub ahead of print, 30 Dec 2019

# NDA for Bimatoprost SR



- New Drug Application filed on 7/17/2019
- Detailed Phase 3 data not yet public, press statement only:

"In the two Phase 3 ARTEMIS studies, Bimatoprost SR reduced intraocular pressure (IOP) by 30% over the 12-week primary efficacy period, meeting the predefined criteria for non-inferiority to the study comparator. The ARTEMIS studies evaluated 1122 subjects on the efficacy & safety of Bimatoprost SR versus timolol, an FDA standard comparator for registrational clinical trials, in patients with open-angle glaucoma or ocular hypertension. After 3 treatments with Bimatoprost SR, greater than 80% of patients remained treatment free & did not need additional treatment to maintain IOP control for at least 12 months. Bimatoprost SR was well tolerated in the majority of patients."

FDA = US Food and Drug Administration.

Press Release. <https://www.allergan.com/news/news/thomson-reuters/u-s-fda-accepts-allergan-s-new-drug-application-fo>.

Accessed January 6, 2020.

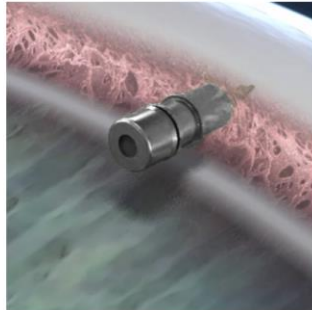
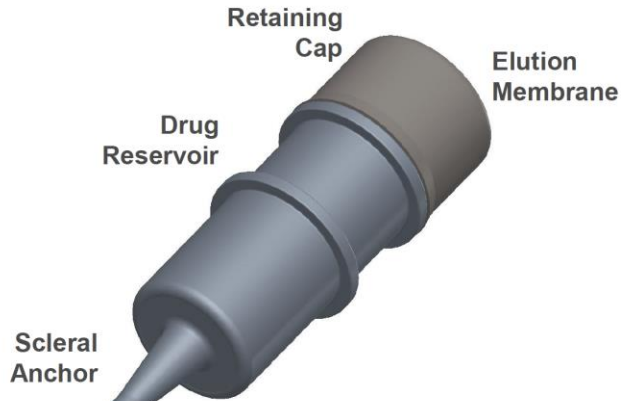
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# Glaukos Travoprost SR device



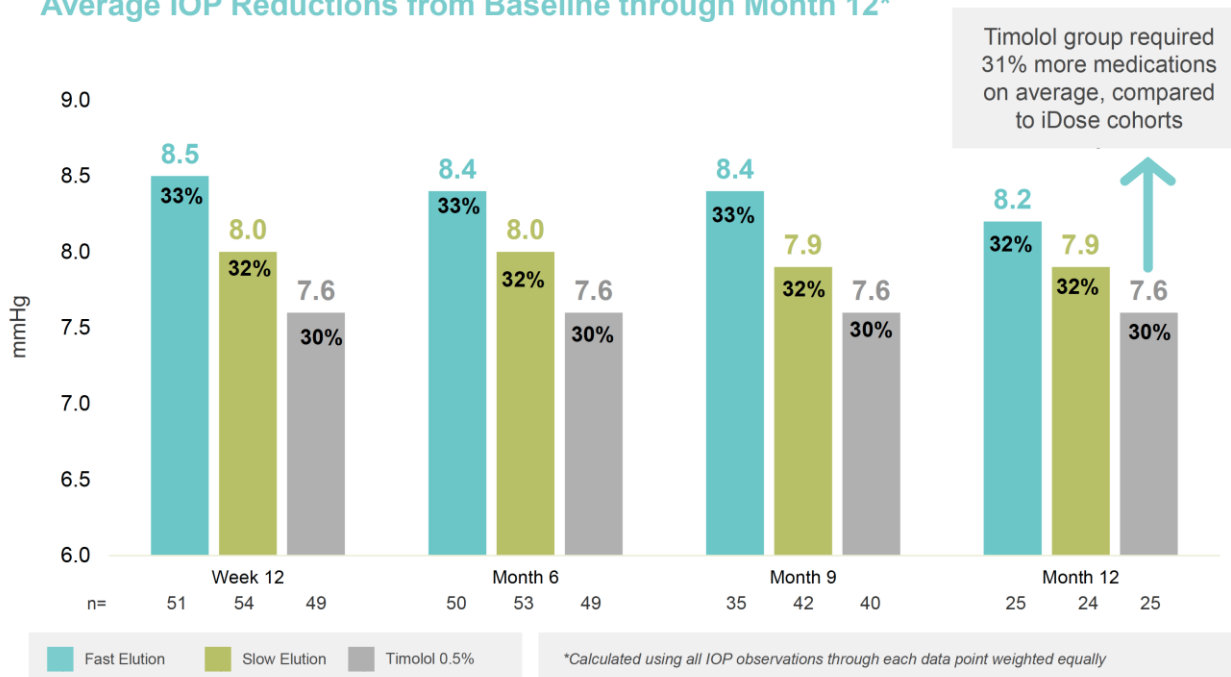
- Titanium implant containing 6+ month supply of travoprost
- Placed and re-placed surgically, anchors in the trabecular meshwork



# Glaukos Travoprost SR device



Average IOP Reductions from Baseline through Month 12\*



ClinicalTrials.gov Data	
Study Design	Prospective multi-center RCT
Comparator	Timolol
Participants	1,000
Actual study start date	22 May 2018
Estimated Primary completion date	June 2021
Estimated Study completion date	June 2023

# Travoprost XR (ENV515)



- Intracameral erodible platform delivering travoprost
- PRINT<sup>®</sup> technology permits production of <100 nm particles to >1 mm implants
- Early Phase 2 data (ARVO 2017\*) demonstrated sustained IOP lowering out to 11 months (5 patients)
- Aerie Pharmaceuticals purchased the rights to PRINT<sup>®</sup> Technology for glaucoma and retinal applications (October 2017)

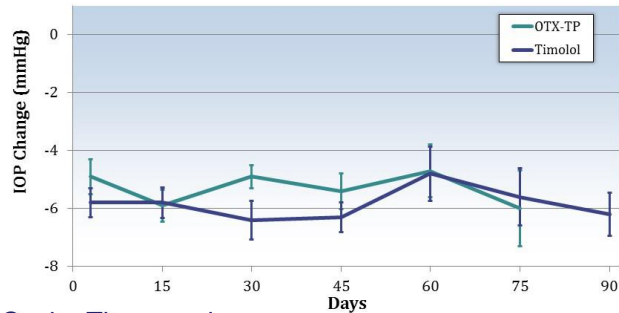
\* Navratil T, Conley J, Verhoeven RS *et al.*  
Extended PGA Delivery Results in Significant Drug Sparing Compared to Topical PGAs and Achieves Sustained IOP Lowering for 11 Months without Any Loss of Efficacy  
ARVO 2017

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# Punctal Plug drug delivery



Source: Ocular Therapeutix  
<http://www.ocutx.com/pipeline/travoprost-punctum-plug>



Source: <http://www.matitherapeutics.com/pipeline>

# Punctal Plug Drug Delivery



Row	Saved	Status	Study Title	Conditions	Interventions	Study Start	Study Completion
1	<input type="checkbox"/>	Completed	<a href="#">A Phase 2 Single-Masked, Randomized Study of Latanoprost PPDS in Ocular Hypertension or Open-Angle Glaucoma</a>	<ul style="list-style-type: none"> <li>Ocular Hypertension</li> <li>Open-Angle Glaucoma</li> </ul>	<ul style="list-style-type: none"> <li>Drug: <b>Latanoprost Punctal Plug</b> Delivery System (L-PPDS)</li> </ul>	December 2013	December 2016
2	<input type="checkbox"/>	Completed	<a href="#">Study of the Effects of Artificial Tears on the Response to the Latanoprost Punctal Plug Delivery System in Subjects With Ocular Hypertension or Open-Angle Glaucoma</a>	<ul style="list-style-type: none"> <li>Glaucoma</li> <li>Ocular Hypertension</li> </ul>	<ul style="list-style-type: none"> <li>Drug: <b>Latanoprost punctal plug</b></li> <li>Drug: artificial tears preserved with Benzalkonium Chloride</li> </ul>	January 2009	December 2009
3	<input type="checkbox"/>	Completed	<a href="#">A Study Evaluating the Latanoprost Punctal Plug Delivery System (L-PPDS) in Subjects With Ocular Hypertension or Open-Angle Glaucoma</a>	<ul style="list-style-type: none"> <li>Ocular Hypertension</li> <li>Open Angle Glaucoma</li> </ul>	<ul style="list-style-type: none"> <li>Drug: <b>Latanoprost-PPDS</b></li> </ul>	October 2010	August 2011
4	<input type="checkbox"/>	Completed	<a href="#">A Safety Study of the Latanoprost Punctal Plug Delivery System (L-PPDS) in Subjects With Ocular Hypertension or Open Angle Glaucoma</a>	<ul style="list-style-type: none"> <li>Glaucoma</li> <li>Ocular Hypertension</li> </ul>	<ul style="list-style-type: none"> <li>Drug: <b>Latanoprost-PPDS</b></li> </ul>	January 2009	December 2009
5	<input type="checkbox"/>	Withdrawn	<a href="#">A Phase 2 Study of the Latanoprost Punctal Plug Delivery System in Subjects With Ocular Hypertension or Open-Angle Glaucoma</a>	<ul style="list-style-type: none"> <li>Glaucoma</li> <li>Ocular Hypertension</li> </ul>	<ul style="list-style-type: none"> <li>Drug: <b>Latanoprost-PPDS</b></li> </ul>	March 2009	July 2009
6	<input type="checkbox"/>	Completed	<a href="#">A Study of the L-PPDS With Adjunctive Xalatan® Eye Drops in Subjects With OH or OAG</a>	<ul style="list-style-type: none"> <li>Ocular Hypertension</li> <li>Open-Angle Glaucoma</li> </ul>	<ul style="list-style-type: none"> <li>Drug: <b>Latanoprost Punctal Plug</b> Delivery System</li> <li>Drug: Xalatan</li> </ul>	December 2009	July 2010
7	<input type="checkbox"/>	Completed	<a href="#">A Dose Evaluation Study for the Latanoprost Punctal Plug Delivery System (L-PPDS) in Subjects With Ocular Hypertension or Open-Angle Glaucoma</a>	<ul style="list-style-type: none"> <li>Glaucoma</li> <li>Ocular Hypertension (OH)</li> </ul>	<ul style="list-style-type: none"> <li>Drug: <b>Latanoprost-PPDS</b></li> </ul>	November 2011	September 2012
8	<input type="checkbox"/>	Completed	<a href="#">A Dose Evaluation Study of the Effect of Plug Placement on the Efficacy and Safety of the Latanoprost Punctal Plug Delivery System (L-PPDS) in Subjects With Ocular Hypertension or Open-Angle Glaucoma</a>	<ul style="list-style-type: none"> <li>Glaucoma</li> <li>Ocular Hypertension (OH)</li> </ul>	<ul style="list-style-type: none"> <li>Drug: <b>Latanoprost-PPDS</b></li> </ul>	November 2011	September 2012
9	<input type="checkbox"/>	Completed	<a href="#">A Phase 2 Study of Punctal Placement of the Latanoprost Punctal Plug Delivery System (L-PPDS)</a>	<ul style="list-style-type: none"> <li>Open-Angle Glaucoma</li> <li>Ocular Hypertension</li> </ul>	<ul style="list-style-type: none"> <li>Drug: <b>Latanoprost</b></li> </ul>	January 2009	November 2009
10	<input type="checkbox"/>	Completed	<a href="#">A Study of Different Formulations of the L-PPDS in Subjects With OH or OAG</a>	<ul style="list-style-type: none"> <li>Glaucoma</li> <li>Ocular Hypertension</li> </ul>	<ul style="list-style-type: none"> <li>Drug: Formulation E1 of L-PPDS</li> <li>Drug: Formulation E2 of L-PPDS</li> </ul>	August 2009	May 2010

# Punctal Plug Drug Delivery



- Only public-facing data from a Phase III pivotal trial for punctal plugs disappointing (diurnal data compared to vehicle):
  - -1.8 mmHg (2 weeks), -0.9 mmHg (6 weeks), -0.6 mmHg (12 weeks)

*OTX-TP failed to meet primary endpoint but achieved statistically significant reduction of intraocular pressure versus placebo at eight of the nine pre-specified time points*

*The Company plans to discuss the data from the clinical trial with the FDA and determine next steps*

May 20, 2019 04:05 PM Eastern Daylight Time

**Table 1: Reduction in Intraocular Pressure (Change from Baseline)**

Diurnal Time points	2 Week			6 Week			12 Week		
	mm Hg		p-value	mm Hg		p-value	mm Hg		p-value
	OTX-TP	Vehicle		OTX-TP	Vehicle		OTX-TP	Vehicle	
8:00 AM	-5.72	-3.88	<.0001	-4.81	-4.01	0.0181	-3.91	-3.52	0.2521
10:00 AM	-4.92	-3.16	<.0001	-4.03	-3.23	0.0077	-3.34	-2.63	0.0234
4:00 PM	-5.22	-3.18	<.0001	-4.16	-3.14	0.0004	-3.27	-2.60	0.0310

*FAS Population (OTX-TP=343 subjects, Vehicle=211 subjects)*

*Least Squares (LS) Means*

# Sustained Release Pipeline



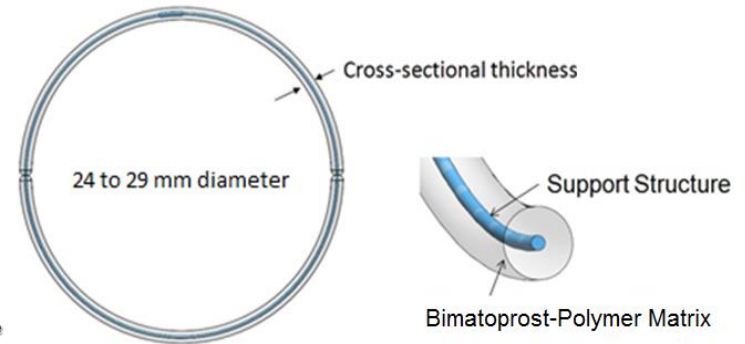
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# Bimatoprost Ocular Insert



- Simple, non-invasive ocular insert – rests under eyelids
- Easily applied by the eye care provider
- Impregnated with bimatoprost; preservative-free
- *Not* bioabsorbable – replaced by physician q6 months
- Can be designed to carry more than 1 drug (bimatoprost + timolol ring recently completed Phase 1)



Brandt JD, Sall K, DuBiner H *et al.*  
Six-Month IOP Reduction with a Topical Bimatoprost Ocular  
Insert: Results of a Phase II Randomized Controlled Study  
*Ophthalmology* 2016;123(8):1685-1694

Brandt JD, Sall K, DuBiner H *et al.*  
Long-term Safety and Efficacy of a Sustained-Release  
Bimatoprost Ocular Ring  
*Ophthalmology* 2017;124(10):1565-1566

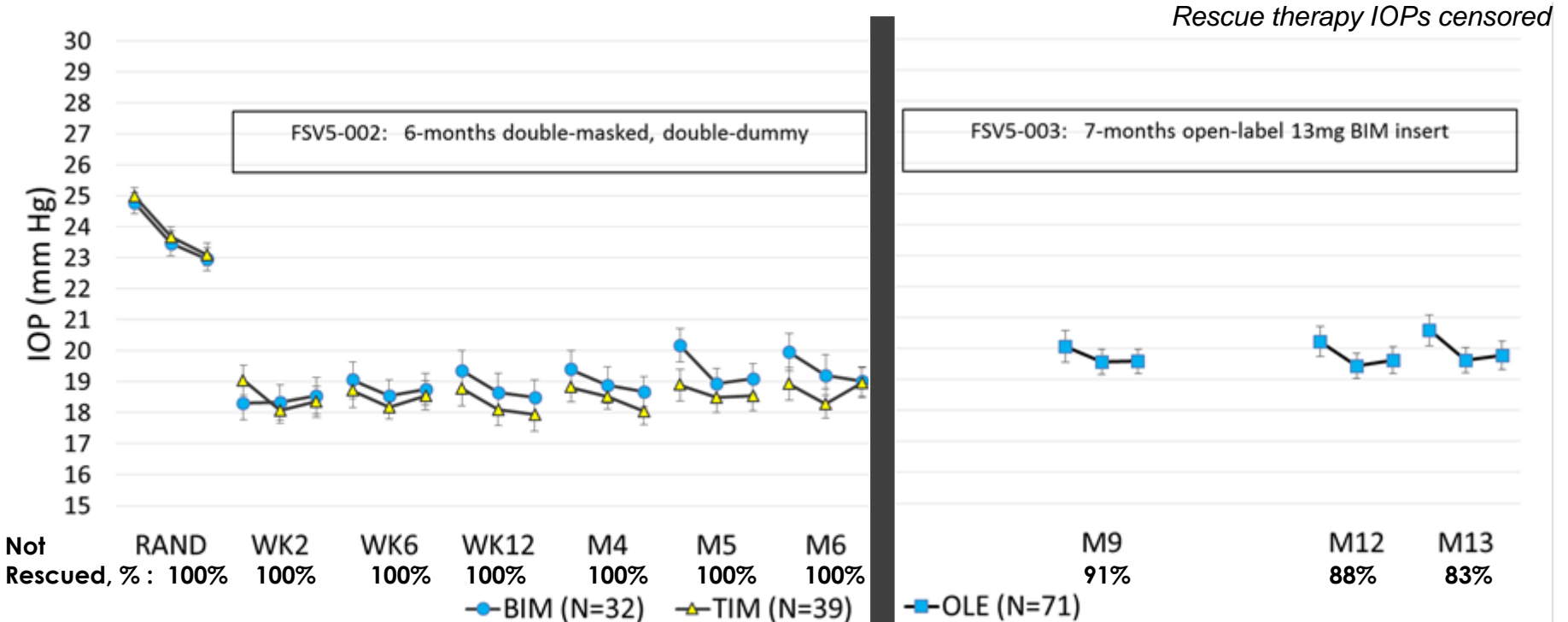


# Placement Procedure



*Filmed at the Sall Research Medical Center*

# Results (Diurnal IOP): Observed Efficacy through 13 months



Brandt JD, Sall K, DuBiner H *et al.*  
Six-Month IOP Reduction with a Topical Bimatoprost Ocular Insert: Results  
of a Phase II Randomized Controlled Study  
*Ophthalmology* 2016;123(8):1685-1694

Brandt JD, Sall K, DuBiner H *et al.*  
Long-term Safety and Efficacy of a Sustained-Release  
Bimatoprost Ocular Ring  
*Ophthalmology* 2017;124(10):1565-1566

# Reality Check



SR Platforms *will* arrive  
in the next 12 – 18 months



# Questions to Ask about ALL Sustained Release Platforms in Development



# Considerations for all SR Platforms



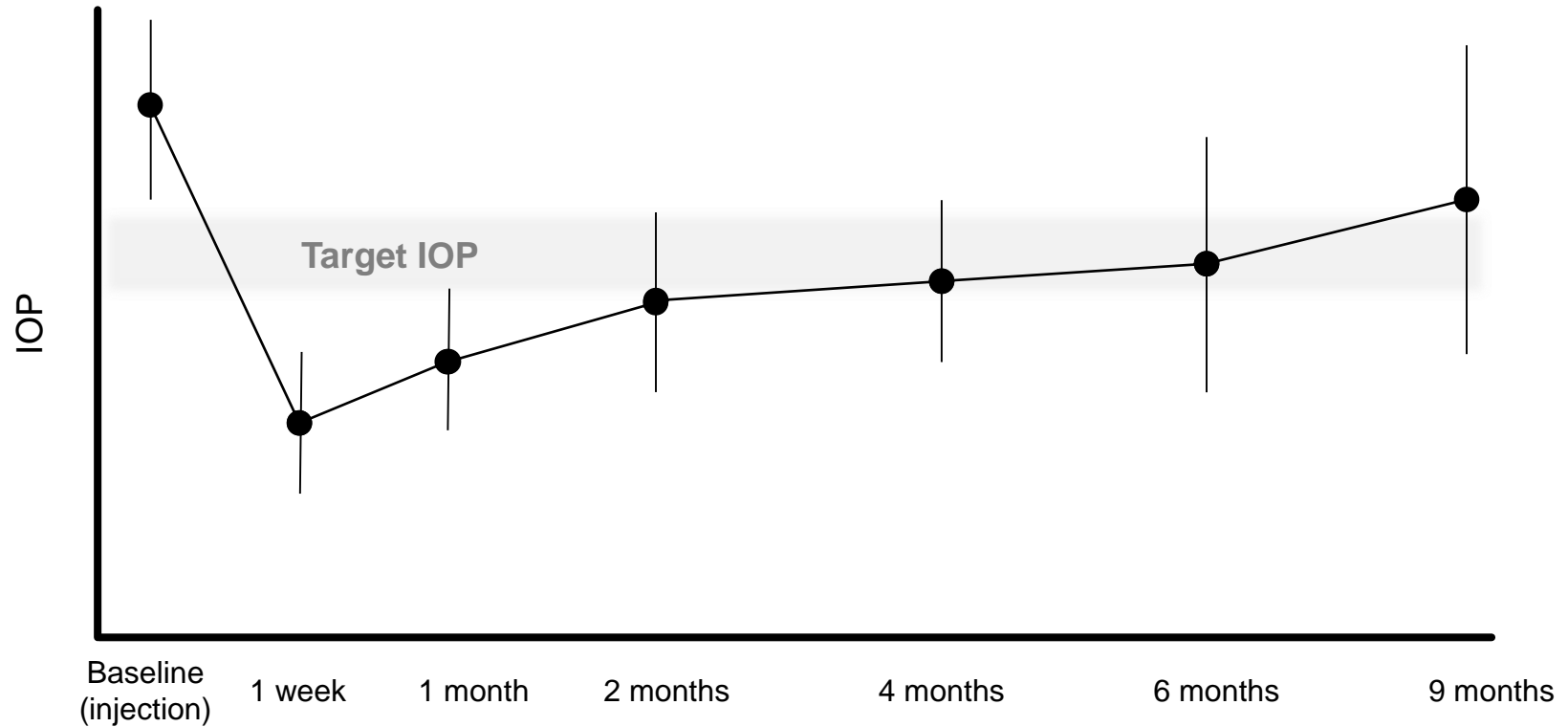
## **How predictable is the duration of action?**

- If a sustained release drug is labeled for 6 months, when do you need to bring patients back for monitoring or re-dosing?

# Duration of action

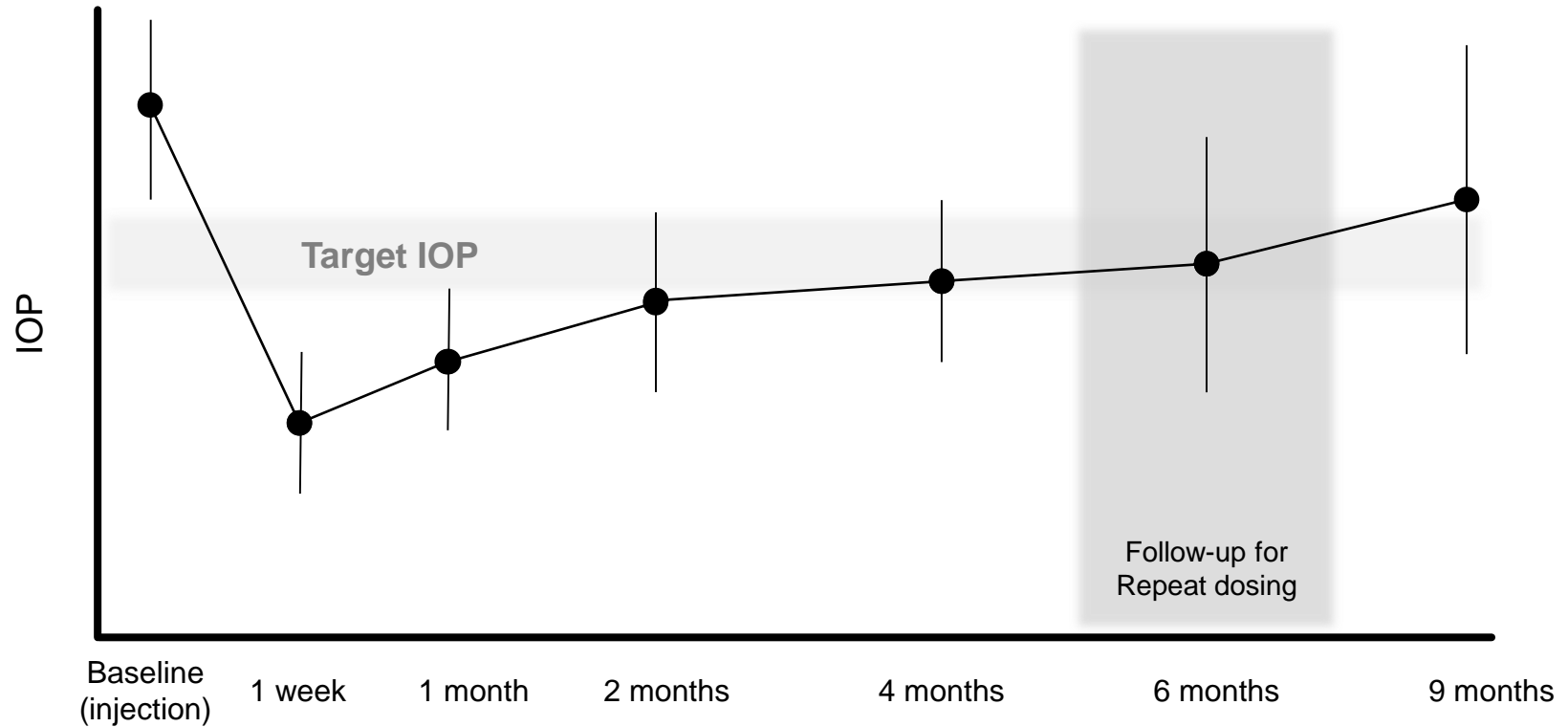


# Duration of action

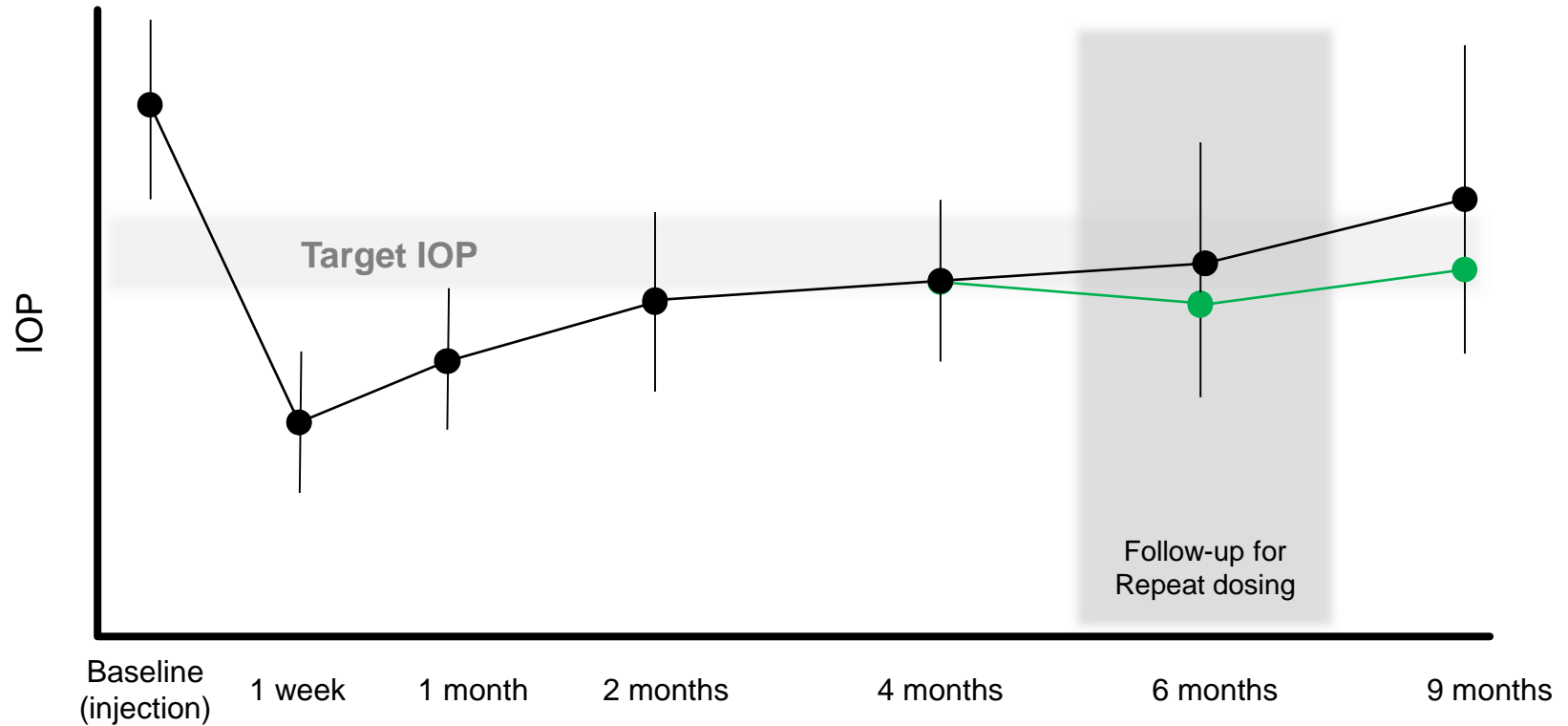




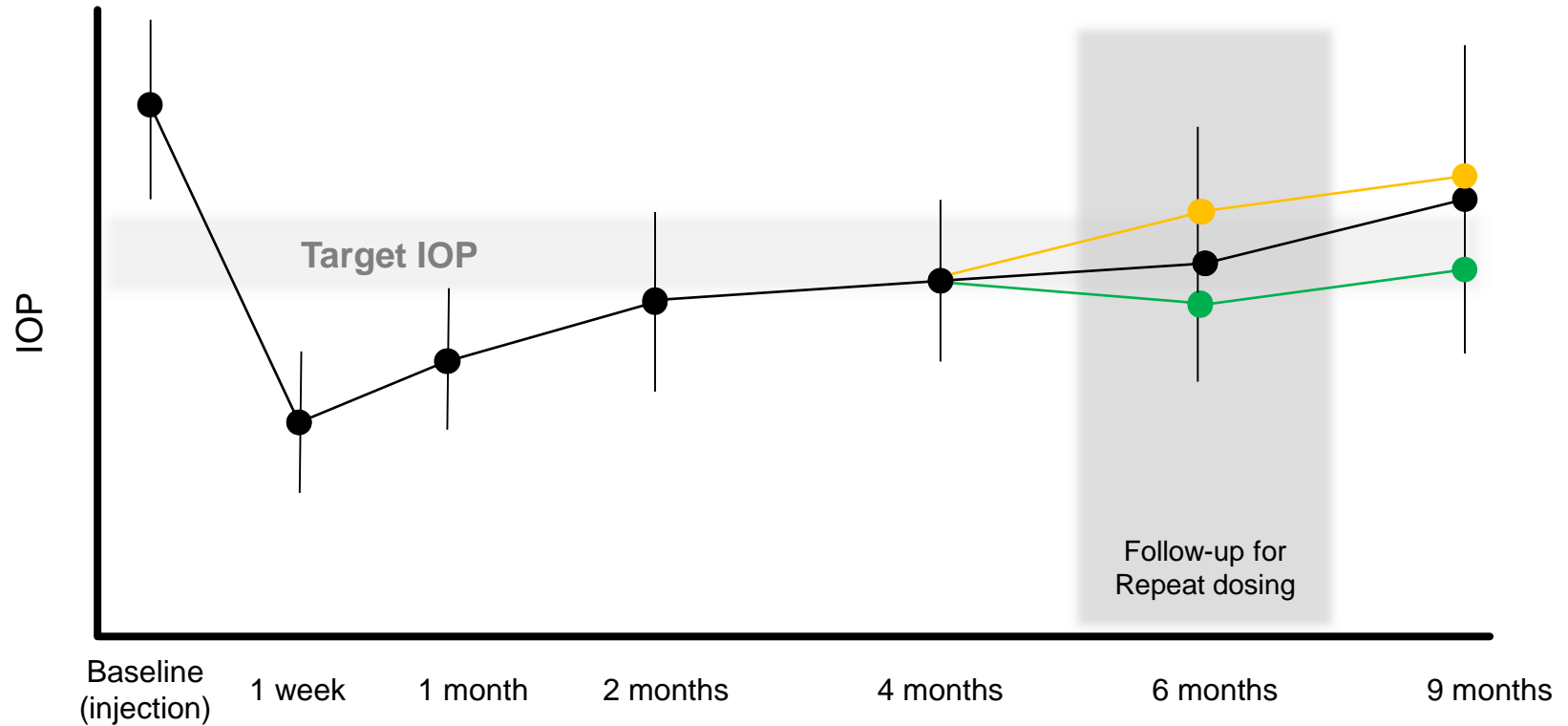
# Duration of action



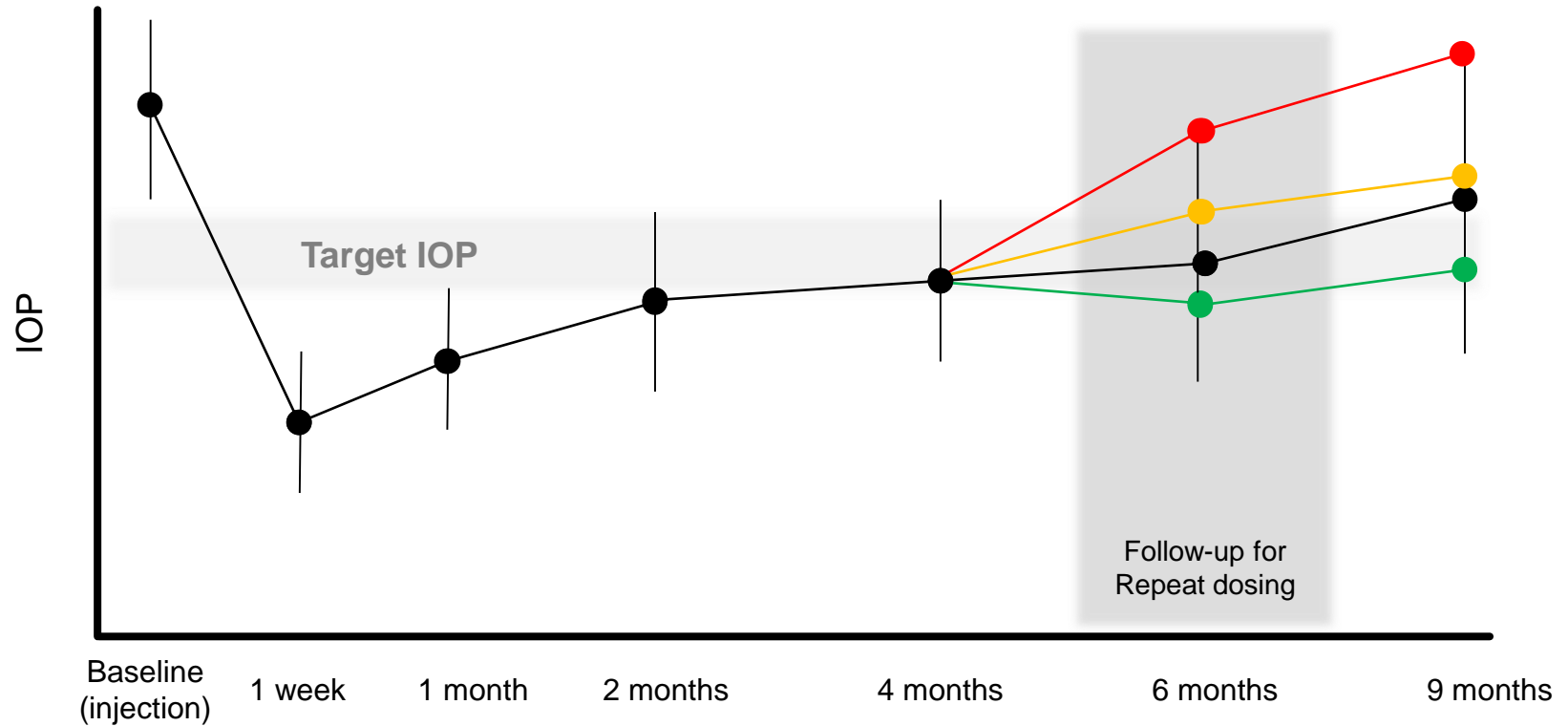
# Duration of action



# Duration of action



# Duration of action



# Considerations for all SR Platforms



## **Glaucoma $\neq$ AMD or DME**

- “Treat & Extend” paradigm won’t work in glaucoma
  - Patients do fall through the cracks & fail to return on time
  - Even poorly-compliant AMD or DME patients will usually initiate a return visit when their vision starts to drop

# Considerations for all SR Platforms



## **Glaucoma $\neq$ AMD or DME**

- Our patients don't know when their IOP is rising
  - Home tonometry may help with this part of the challenge



# Considerations for all SR Platforms



## **What if the patient has a drug side-effect?**

- All SR platforms in the pipeline use one of the three major PGAs
- Eyes at risk of CME were excluded from pivotal trials

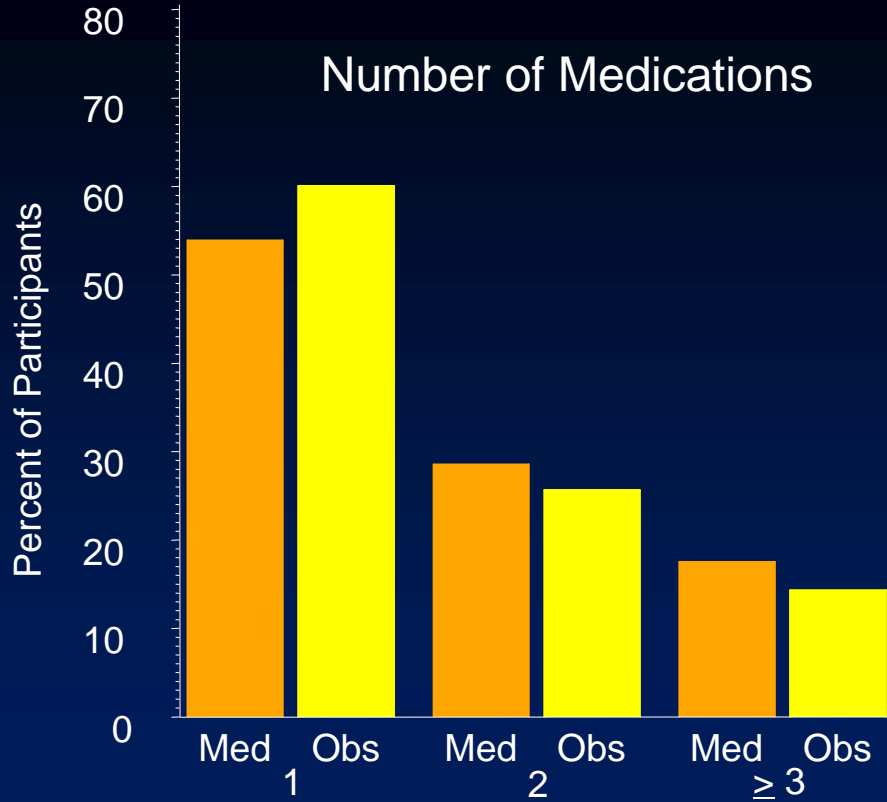
# Considerations for all SR Platforms



**What if the patient needs  
more than one drug?**



# OHTS



- Despite its modest (20%) IOP target, ~ 50% of OHTS subjects required 2 or more medications to reach target
- This was true even for those originally in the observation group, who were started on PGAs half way through the study



# Considerations for Injectables



## Workflow concerns

- Glaucoma is usually bilateral
  - Each patient will typically need 2 injections
  - Will you inject both eyes on the same day?
- What about patients requiring multiple drugs?

## Safety Concerns

- How many injections can a cornea take?
  - Platform(s) may remain months after drug is gone
- Effect on endothelial counts?
- Cumulative risk of endophthalmitis

# Considerations for Injectables



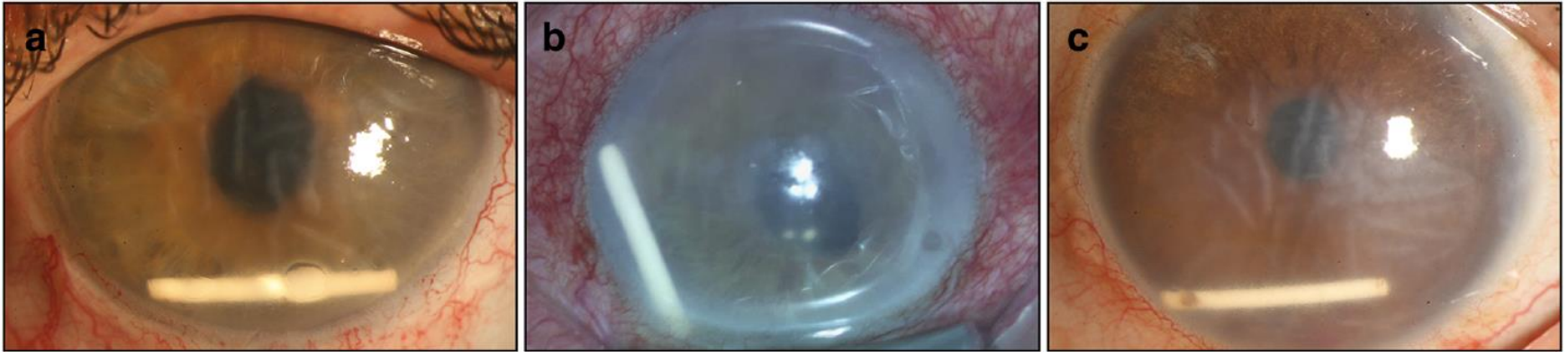
## **What if a pellet migrates?**

- Patients with open capsules or unstable IOLs were excluded from the pivotal trials

# Considerations for Injectables



## What if a pellet migrates?



**Fig. 1** Slit-lamp photography showing the dexamethasone implant dislocated to the inferior angle of the anterior chamber, touching the corneal endothelium, in three different patients (a–c). Diffuse corneal edema and Descemet membrane folds can be seen

Röck D, Bartz-Schmidt KU & Röck T

Risk factors for and management of anterior chamber intravitreal dexamethasone implant migration

*BMC Ophthalmol* 2019;19:120 [open access]

# Considerations for Injectables



## What if a pellet migrates?

- Will it be safe to do a Nd:YAG capsulotomy in a patient with a pellet in place?
- Will you go to the OR to remove a pellet or implant from a patient developing CME?

# Conclusions



# Are Eyedrops Dead?



# Are Eyedrops Dead?



- Serious hurdles to adoption will have to be sorted out, *e.g.*
  - Safety
  - Frequency & timing of office visits
  - Clinic flow & logistics
  - Reimbursement models



# Are Eyedrops Dead?



Eyedrops aren't going away soon...

... but today's pace of innovation suggests that by 2030, eyedrops will *not* be the primary method of glaucoma treatment, supplanted by:

- SR platforms
- Primary SLT\*
- Better stand-alone MIGS

\* Gazzard G, Konstantakopoulou E, Garway-Heath D *et al.* Selective laser trabeculoplasty versus eye drops for first-line treatment of ocular hypertension and glaucoma (LIGHT): a multicenter randomized controlled trial  
*Lancet* 2019; 393:1505-1516



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