New Therapeutics Update

- Eric E. Schmidt, O.D., F.A.A.O.
- President, Omni Eye Specialists
- Founding Partner, KeplrVision
- schmidtyvision@msn.com

1

Eric E. Schmidt, O.D., F.A.A.O.

-
- Disclosures
- Allergan- Consultant, Advisory Board
- Topcon - Consultant
- Tarsus - Consultant
- Eyenovia – Consultant
- Thea Labs- Consultant
- Trukera - Consultant
- Visus – Consultant
- B&L – Consultant
- M&S Technology- Consultant

2

3

But really, is there anything new????

4

Glaucoma Drugs – Tapping that Pipeline!!!

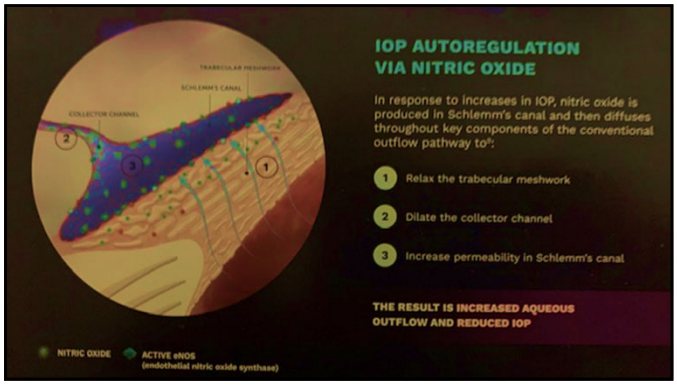
- Nothing New For A While, and then…
  BOOOM!
- Rhopressa
- Rocklatan
- Vyzulta
- But those are so 2019!!
- Anything else??

5

Vyzulta -

- Latanoprostene bunod (0.024%) – B&L
- Is this the new It Girl of the PGA world??

6



7

Vyzulta – A different kind of PGA

- Reduces IOP by 32%
- 1.2mm HG lower than latanoprost
- Preserves VF better by 10%
- No loss of effect while sleeping
- Improved side effect profile
- Releases nitric oxide at the trabecular meshwork level

8

Vyzulta – Brand New Data

- Effect of latanoprostene bunod on Optic Nerve Head Flow
  - Samaha, Diaconu et al, IOVS, Feb 2022, Vol 9, Iss 2 pp172-176
  - Purpose was to evaluate effect of latanoprostene bunod on optic nerve blood volume and O2 saturation – *IN HEALTHY SUBJECTS*
  - Measurements were taken before initiating therapy and then 7 days after QD therapy of both Latanoprost and latanoprostene bunod

9

Study results

- ONH saturated O2 levels were 4% higher with Vyzulta than latanoprost
- ONH blood volume was way higher with Vyzulta
  - 66% higher at Hr 1, 45% higher at Hr 2
- What is the clinical significance of this?

10

Rhopressa (netarsudil) – Aerie Pharmaceuticals

- New class of drugs – Rho-kinase inhibitor
- MOA – "Triple Action"
- - relaxes trabecular meshwork similar to pilocarpine (enhances outflow)
- - lowers episcleral venous pressure
- - blocks fibrotic response at t.m.(increases perfusion)
- QD dosing
- Looks especially effective at IOP 25 mmHg or less

11

Rhopressa (netarsudil) -MOA

Works at the cellular level within the trabecular meshwork

ROCK inhibitors improve outflow by relaxing contraction and stress fibers at the t.m.

12

What Do We Know About Rhopessa (netarsudil 0.02%)

- Rhopressa QD is non-inferior to timolol 0.5% BID in lowering IOP
- Expected IOP reduction 3.7 -7.0mm Hg
- Rhopressa seems to better at lowering IOP (as compared to itself) in pressures < 25mm Hg
- IOP lowering effect is maintained over 12 months
- Was given a broad label by FDA

13

Rhopressa – Adverse Effects

- Generally well tolerated
- Conjunctival hyperemia – 53%
  - Did not worsen with time
  - Mild-36.8%, moderate – 10.5%, severe -0.6%
  - D/C rate due to redness -~3%
- Corneal verticillata – 18%
- Conjunctival hemorrhage – 15%
  - All are transient and considered mild

14

What's to like about Rhopressa?

- New MOA so… it is absolutely different
- It should be additive
- Definitely works better at lower IOP
- What about side effects?

15

Rhopressa- some thoughts

- How are you positioning it in your practice??
- What are our clinical experiences 2 years later?
- Is it a first line drug?
- What about insurance coverage?
- What color top does it have??

16

Update on Rhopressa

- Relaxes Actin & Myosin fibers > Increases outflow at t.m.
- Yields 35% Improvement in tm outflow in glaucoma patients (vs 20% improvement in normal)
- Excellent response on episcleral venous pressure- netarsudil reduces EVP by 10% - no other drop achieves this
- No longer needs to be refrigerated after opening

17

M.O.S.T. Study

- Real World Open Label Phase 4 Study
- ASCRS 2020
- To determine efficacy of Rhopressa as an adjunct med
- Investigator's Choice – Rhopressa + any other agent
- 24.4% African-American participants

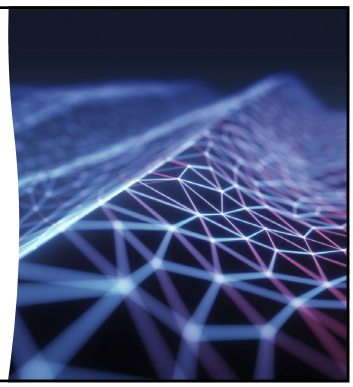
18

M.O.S.T. Results

Rhopressa + PGA - IOP 21.1> 16.9 mmHg (20% reduction)

Rhopressa + 2 meds – 20.6 > 16.6 mmHg (20% reduction)

Notice the low baseline IOP



19

More M.O.S.T. Results

- % of pxs less than < 18mm Hg
  - <18mm -72.7 % (from 34.4%)
  - <17mm- 65% (from 25.2%)
  - <15mm -40.6% (from 15.9%)
  - <14mm- 30.1% (from 11.3%)
- 2/3 of all patients achieved IOP < 17mm Hg

20

M.O.S.T. Tolerability rates

Hyperemia – 20.* %

D/C rate – hyperemia 3.4%

Tolerability rating

67.8-73.1% good or decent (physician response)

65-78% good or decent (Patient response)

21

Roclatan – Aerie

- Fixed Combination drug – Rhopressa + latanoprost
- QD dosing
- "Quadruple acting" MOA – (adds increased uveoscleral outflow)
- IOP lowering better than either of its components
- Potential to be very effective – lowered IOP an additional 2-3 mm compared to Rhopressa (and other PGAs)

22

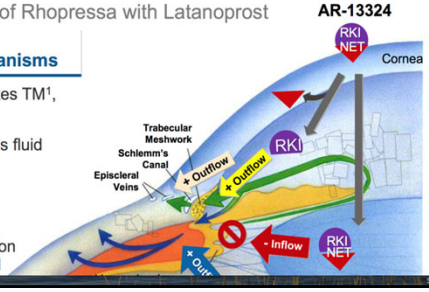
Roclatan™ (netarsudil/latanoprost ophthalmic solution) 0.02%/0.005%

Fixed Combination of Rhopressa with Latanoprost

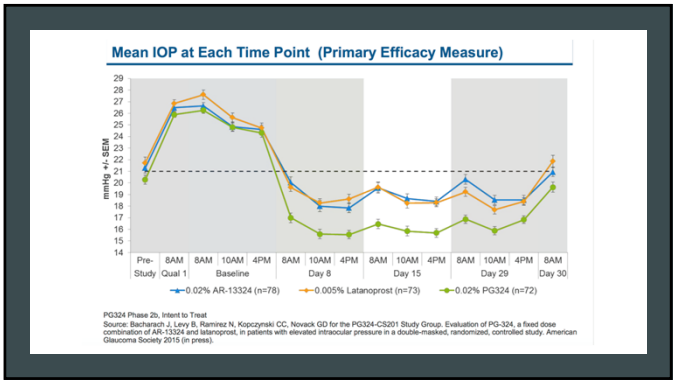
AR-13324

4 Identified IOP-Lowering Mechanisms

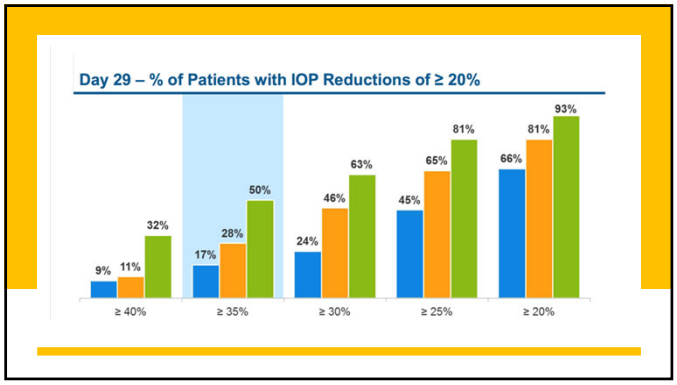
- ROCK inhibition relaxes TM[1], increases outflow[1,2]
- NET inhibition reduces fluid production[2]
- ROCK inhibition lowers EVP[3]
- PGA receptor activation increases uveoscleral



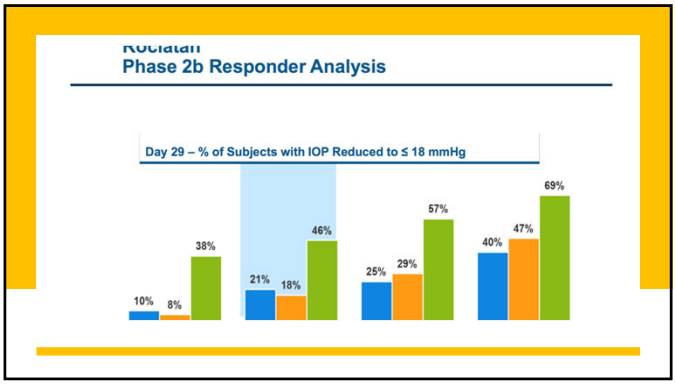
23



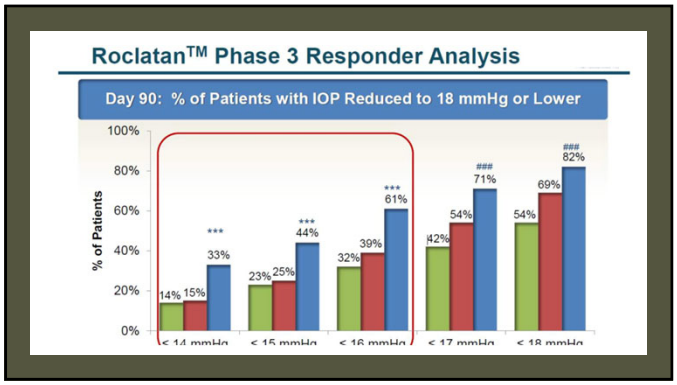
24



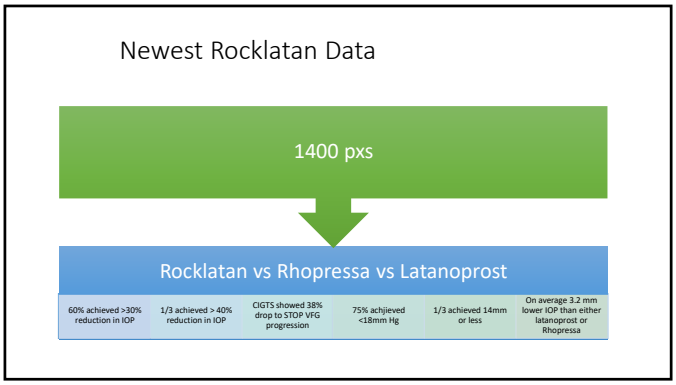
25



26



27



28

Newest side effect data

- No tachyphylaxis at 12 months
- No unexpected A.E.
- Very few serious A.E.- majority are mild

- 58% hyperemia but 5% d/c rate
- 20% Instillation pain – 0% d/c
- 10% subconj heme – 0% d/c

29

But really… Is There Anything New??

Iyuzeh-
(latanoprost 0.005%)

Thea Pharmaceuticals

Let's talk about this…

30

Iyuzeh (latanoprost 0.005%)

- Does that sound familiar?
- Monoprost (in Europe) – the market leader in PGA in Europe
- This actually is PRESERVATIVE FREE latanoprost!!
- Single dose container
- But does it really work??

31

Iyuzeh – Phase 3 data

- Compared to Xalatan (Switch Study)
- Stable POAG pxs on Xalatan
- 8 day washout period
- 3 months on Iyuzeh
- IOP reduction was 4-8mm Hg on Xalatan
- IOP reduction was 3-8mm Hg on Iyuzeh
- Baseline IOP was 19mmHG!!

32

Iyuzeh – Phase 3 data- Adverse Effects

- Xalatan group
  - Hyperemia – 31%
  - Eye Irritation – 34%
- Iyuzeh Group
  - Hyperemia – 34%
  - Eye irritation – 19%
- ZERO reports of SPK

33

Subsequent Iyuzeh studies

- European data – Higher baseline IOP (24mm Hg)
  - IOP lowered to 15.5mm Hg
  - Same rate of adverse effects
- Bachrach data (2023 AGS)
  - 12 week trial comparing to Xalatan
  - Similar IOP reduction (as measured by ability to get IOP <18mm Hg)
  - 2% experienced redness or ocular irritation
  - 0% SPK

  Fewer ocular side effects (13.9% vs 22.5%)
- PASSY study
  - 97% tolerated drop
  - AT usage decreased 24%

34

#What's The Big Deal??

- OSD is an epidemic in glaucoma
- Will this improve compliance?
- Will this cost $1M??
- Is it better than what we have?

35

So, a patient on latanoprost needs 4 more mm of IOP reduction- do you…

- Add Rhopressa?
- Switch to Rocklatan??
- Add a combo drop??
- Switch to a combo drop??
- Switch to another PGA?
- SLT??

36

One final word about glaucoma therapies

A lot of money is being spent on delivery systems

These may be cheaper alternatives

Optometry cannot sleep on this

37

Automated Direct SLT (Belkin)

38

Belkin DSLT

- Rapid, non-contact Direct SLT
- Delivers similar energy as traditional SLT
- Automated delivery of energy through limbus (transconjunctival)
- Without Gonioscopy
- Will be approved in US within months!!

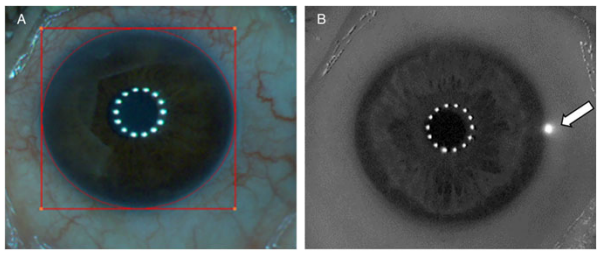
39

DSLT Data

- Baseline IOP 26.7-
  - Patients were washed out of all meds
  - Some pxs were treatment naïve
- After tx IOP
  - 1 mth – 21.7mm Hg (18.1% reduction)
  - 3 mth- 20.8mm HG (21.4%)
  - 6 mth 21.5mm Hg (18.8% reduction)
- At 6 mths medication need reduced from 1.6 to 0.4

40

Automated Direct SLT



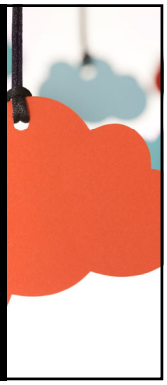
41

#This Is A BFD!!

Are we ready???

42

Now Let's Have a Talk About The Heartbreak of Demodex!!



43

DEMODEX BLEPHARITIS

- **Blepharitis is inflammation of the eyelids** causing irritation and redness
- **69% of blepharitis cases are due to *Demodex* infestation leading to *Demodex* blepharitis[1-4]**
  - *Demodex* mites are implicated in other diseases of the lid and lid margin, including blepharitis and meibomian gland dysfunction[2,3]
  - *Demodex* mites are associated with acne vulgaris, folliculitis, rosacea, seborrheic dermatitis, perioral and scalp hair loss, and basal cell carcinoma[1,3]
- ***Demodex folliculorum* and *Demodex brevis*** are the only 2 species found in humans[5]
  - The life cycle of the *Demodex* mite is approximately 14 to 18 days from the egg to the larval stage followed by the adult stage[5]
  - The life span of the mite is limited outside the living body;

D. folliculorum

0.3-0.4 mm length
Colonizes the base of the lash follicle[2]

D. brevis

0.1 mm length
Colonizes the meibomian gland[2]

1. Mayo Clinic. Accessed June 28, 2022. https://www.mayoclinic.org/diseases-conditions/blepharitis/symptoms-causes/syc-20370141 2. Zhang AC et al. *Ophthalmic Physiol Opt.* 2020;40(4):389-432. 3. Fromstein SR et al. *Clin Optom (Auckl).* 2018;10:57-63. 4. Trottier W et al. *Clin Ophthalmol.* 2022;16:1153-1164. 5. Litwin D et al. *Iran J Parasitol.* 2017;12(1):12-21.

45

DEMODEX BLEPHARITIS | MECHANISMS OF DISEASE

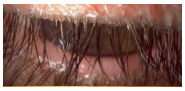
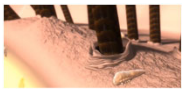
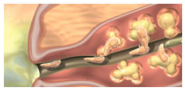


Image courtesy of Laura M. Periman, MD, used with permission.*





MECHANICAL

- Lash distension occurs as *Demodex* mites attach to follicles[2-4]
- *Demodex* mites deposit debris and digestive enzymes, causing further irritation to the eyelid margin[4,5]

BACTERIAL

- *Demodex* mites can contribute to blepharitis by carrying bacteria on their exterior surface that may elicit immune responses[3,6-7]

CHEMICAL

- *Demodex* mites have been associated with altered meibum composition[8]
- Debris from *Demodex* mites can potentially lead to chronic inflammation and degeneration of conjunctival tissue[9]

1. Data on file. Images courtesy of Laura M. Periman, MD; 2022. 2. Zhang AC et al. *Ophthalmic Physiol Opt.* 2020;40(4):389-432. 3. Liu J et al. *Curr Opin Allergy Clin Immunol.* 2010;10(5):505-510. 4. Fromstein SR et al. *Clin Optom (Auckl).* 2018;10:57-63. 5. Gao YY et al. *Invest Ophthalmol Vis Sci.* 2005;46(9):3089-3094. 6. Zhu W et al. *Front Microbiol.* 2018;9:1719. 7. Li J et al. *Ophthalmology.* 2010;117(5):870-877. 8. Gao Y et al. *Transl Vis Sci Technol.* 2019;8(1):4-14. 9. Tarkowski W et al. *Biomed Res Int.* 2021;2560509.

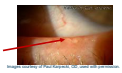
46

CLINICAL MANIFESTATIONS OF *DEMODEX* BLEPHARITIS

Images courtesy of Paul Karpecki, OD, used with permission.

Disorders of Eyelashes[1,2]

Infestation of the lash follicles can result in collarettes and may lead to malalignment, trichiasis, and madarosis



Images courtesy of Paul Karpecki, OD, used with permission.

Meibomian Gland Dysfunction[1,2]

Blockage leads to filling, swelling, and many enlarged glands (cysts) or infection. Chalazia are common granulomatous responses

Lid Margin Inflammation[1,2]

Severe lid margin inflammation can be caused by mechanical blockage and a delayed host immune hypersensitivity reaction

Images courtesy of Ellen Kramer, OD, used with permission.

Conjunctival Inflammation[1,2]

Without proper hygiene, lid margin inflammation may spread over to the conjunctiva producing a condition known as blepharoconjunctivitis

Corneal Manifestations[1,2]

D. brevis is commonly associated with inflammation that spreads to the cornea, causing sight-threatening corneal lesions, superficial vascularization, marginal infiltrates, phlyctenule-like lesions, opacity, and/or nodular scars

1. Liu J et al. *Curr Opin Allergy Clin Immunol.* 2010;10(5):505-510 2. Cheng AM et al. *Curr Opin Ophthalmol.* 2015;26(4):295-300.

47

COLLARETTES ARE A PATHOGNOMONIC SIGN OF *DEMODEX* BLEPHARITIS

Collarettes, or cylindrical dandruff, are composed of mite waste products and eggs[1]

- Collarettes are translucent, solidified exudative excretions that form a cylindrical collar that cuffs around the base of the eyelash follicle[1-3]
- Collarettes are displaced along the shaft of the lash as it grows, and they are also displaced due to bacterial overgrowth[4]
- Collarettes are composed of regurgitated undigested mite waste combined with epithelial cells, keratin, mite eggs, and secreted proteases and lipases that cause irritation[3]
- **100%** of patients with collarettes have *Demodex* blepharitis[2,5]

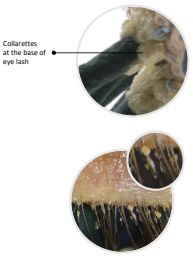


Image courtesy of Inder Paul Singh, MD, used with permission.*

1. Zhang AC et al. *Ophthalmic Physiol Opt.* 2020;40(4):389-432. 2. Gao YY et al. *Invest Ophthalmol Vis Sci.* 2005;46(9):3089-3094. 3. Fromstein SR et al. *Clin Optom (Auckl).* 2018;10:57-63. 4. Bitton E et al. *Clinical and Experimental Optometry.* 2021;104(3):285-294. 5. Karantsoulas N et al. *Int J Ophthalmol.* 2017;10(1):122-127. 6. Data on file. Image courtesy of Inder Paul Singh, MD; 2022.

48

Collarettes = *Demodex* blepharitis

- Collarettes are the pathognomonic sign of *Demodex* blepharitis[1]
  - Symptoms may overlap with those of ocular surface diseases, such as dry eye or allergies[1,2]
- **100% of patients with collarettes are found to have *Demodex* mites[3]**
- Collarettes are composed of mite waste products, eggs, and digestive enzymes, all of which cause irritation[1]

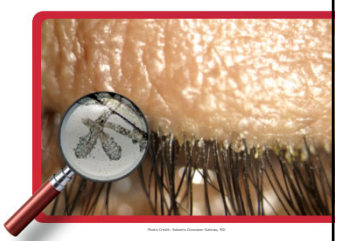


Photo Credit: Roberto Gonzalez-Salinas, MD

References: 1. Fromstein SR, Harthan JS, Patel J, Opitz DL. *Demodex blepharitis: clinical perspectives. Clin Optom (Auckl).* 2018;10:57-63. **2.** Ocular allergies. American Optometric Association. Accessed September 14, 2022 https://www.aoa.org/healthy-eyes/eye-and-vision-conditions/ocular-allergies?sso=y **3.** Gao YY, Di Pascuale MA, Li W, et al. High prevalence of *Demodex* in eyelashes with cylindrical dandruff. *Invest Ophthalmol Vis Sci.* 2005;46(9):3089-3094.

DEMODEX BLEPHARITIS IS PREVALENT IN YOUR EYE CARE CLINICS

***Demodex* blepharitis may be as prevalent as dry eye disease**

Titan study of 1032 patients in 6 OD/MD centers using collarettes for diagnosis[1,*]

Percent of overall population

Two-center study of 199 patients in New York using eyelash epilation for diagnosis[2,†]

Percent of overall population

Diagnosing *Demodex* blepharitis via slit lamp (collarettes) or lash epilation results in similar prevalence. Collarettes are a pathognomonic sign of *Demodex* blepharitis

*Per an IRB-approved retrospective chart review of 1032 patients examined for collarettes across 6 US eye care clinics.
†Per a prospective, cross-sectional study of 199 patients, where the prevalence and risk factors for *Demodex* blepharitis were examined across 2 tertiary care outpatient ophthalmology clinics and mites were confirmed via epilation.
IRB, institutional review board; MD, Doctor of Medicine; OD, Doctor of Optometry.
‡The calculator implements an unpublished algorithm that is based on data from a prospective case series of over 200 patients.
1. Trattler W et al. *Clin Ophthalmol*. 2022;16:1153-1164. 2. Teo A et al. *Invest Ophthalmol Vis Sci*. 2021;62(8):1236.

49

DEMODEX BLEPHARITIS IS PREVALENT IN YOUR EYE CARE CLINICS

***Demodex* mites are the leading cause of blepharitis**

Titan study of 1032 patients in 6 OD/MD centers using collarettes for diagnosis[1,*]

Percent of blepharitis patients due to *Demodex* mites

Two-center study of 199 patients in New York using eyelash epilation for diagnosis[2,†]

Percent of blepharitis patients due to *Demodex* mites

Diagnosing *Demodex* blepharitis via slit lamp (collarettes) or lash epilation results in similar prevalence. Collarettes are a pathognomonic sign of *Demodex* blepharitis

*Per an IRB-approved retrospective chart review of 1032 patients examined for collarettes across 6 US eye care clinics.
†Per a prospective, cross-sectional study of 199 patients, where the prevalence and risk factors for *Demodex* blepharitis were examined across 2 tertiary care outpatient ophthalmology clinics and mites were confirmed via epilation.
IRB, institutional review board; MD, Doctor of Medicine; OD, Doctor of Optometry.
1. Trattler W et al. *Clin Ophthalmol*. 2022;16:1153-1164. 2. Teo A et al. *Invest Ophthalmol Vis Sci*. 2021;62(8):1236.

50

PREVALENCE OF COMORBIDITIES IN PATIENTS DIAGNOSED WITH *DEMODEX* BLEPHARITIS

Patients that presented with collarettes (%):

Cataracts[1]	On dry eye prescription[1]	Glaucoma[1]	Meibomian gland dysfunction[1]	Contact lens wearers[1]	Facial rosacea[6]
56%	**60%**	**65%**	**57%**	**51%**	**60%**
In cataract surgery patients, *Demodex* infestation exacerbates dry eye symptoms[2]	Delayed diagnosis of *Demodex* blepharitis in patients with dry eye disease can have a psychosocial impact[3,4]	*Demodex* blepharitis in glaucoma patients exacerbates ocular surface disease and may lead to treatment intolerance[1]	Meibomian gland dysfunction linked to *Demodex* infestation leads to tear film perturbations and the appearance of hordeola and chalazion	*Demodex* positivity exceeds 90% in contact lens–intolerant individuals, causing discomfort[5]	Searching for *Demodex* infestation in the eyelash follicles of patients diagnosed with rosacea can impact management and potentially modify the course of disease[6]

***Demodex* blepharitis is present in some of your most commonly seen patients**

1. Trattler W et al. *Clin Ophthalmol*. 2022;16:1153-1164. 2. Nowomiejska K et al. *J Clin Med*. 2020;9(10):3069. 3. O'Dell L et al. Psychosocial impact of Demodex blepharitis. *Clin Ophthalmol*. 2022; 16:2979-2987. 4. Fromstein SR et al. *Clin Optom (Auckl)*. 2018;10:57-63. 5. Turkowski W et al. *Biomed Res Int*. 2015;259108. 6. Gonzalez-Hinojosa D et al. *Indian J Ophthalmol*. 2018;66(1):36-38.

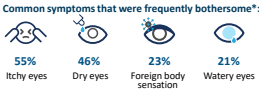
51

THE NEGATIVE BURDEN OF *DEMODEX* BLEPHARITIS IS VERY REAL

80% of patients report negative impact on daily life*

- **Atlas** multicenter, observational study (N=311)
- Evaluated the clinical and patient-reported impact of *Demodex* blepharitis
- Inclusion criteria:
  - At least 1.0 mites per lash
  - >10 collarettes on the upper eye lid
  - At least mild erythema (redness)

Common symptoms that were frequently bothersome*:



51% Experienced signs and symptoms ≥4 years

58% Never diagnosed with blepharitis

33% Made at least 2, and sometimes >6, visits to a doctor for this condition

*Per an observational study of adult *Demodex* blepharitis patients from 8 US ophthalmic and optometric centers.
O'Dell L, Danker DS, Davries DK et al. Psychosocial impact of Demodex blepharitis. *Clin Ophthalmol*. 2022;16:2979-2987.

52

WELCOME XDEMVY (LOTILANER 0.25%)- TARSUS PHARMACEUTICALS

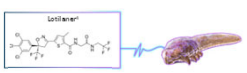
- Only known treatment to eradicate Demodex mites
- Preserved topical drop
- BID x 6 weeks
- Effect lasts up to 1 year

53

MECHANISM OF ACTION OF TP-03 (Lotilaner Ophthalmic Solution, 0.25%)

TP-03 : Lotilaner ophthalmic solution 0.25% (Tarsus Pharmaceuticals, Inc.)

- Lotilaner functions as a noncompetitive antagonist of mite and arachnid GABA-gated chloride channels[1,2]
- Directly paralyzes the mite nervous system through parasite-specific GABA inhibition, leading to death[1,2]
- The lipophilic nature of the drop suggests its ability to flow into the oily sebum of the lash follicle where the mites reside[3]



Product form[5]
Preserved (sorbate) multidose eye drop solution in bottle

Dosing[5]
Twice daily for 6 weeks

FDA, Food and Drug Administration; GABA, gamma aminobutyric acid.
1. Dailymed Credelio. Accessed June 28, 2022. https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=427f2ebc-ce24-452b-b8b3-43d4ef8b62b3 2. Gonzalez-Salinas R et al. *J Ophthalmol*. 2021:3862684. 3. Liarildo. Accessed June 28, 2022. https://www.globenewswire.com/news-release/2022/05/02/2434549/0/en/Liarildo-Partner-Tarsus-Pharmaceuticals-Announces-Positive-Topline-Data-from-Second-Pivotal-Trial-of-TP-03-for-the-Treatment-of-Demodex-Blepharitis.html
4. ChemSrc Lotilaner. Accessed June 28, 2022. https://www.chemsrc.com/en/cas/1638863-73-0_1262257.html 5. Yeu E et al. Cornea. 2022;in Press.

54

SATURN-1 AND SATURN-2 | PIVOTAL CLINICAL STUDIES OF TREATMENT FOR *DEMODEX* BLEPHARITIS

Consistent cures and **responses** demonstrated in **2 pivotal trials,** the largest clinical program for *Demodex* blepharitis, involving **833 patients**

The primary and all secondary endpoints (collarette cure, mite eradication, lid erythema) met with high statistical significance

Clinically and statistically significant effects seen as early as **2 weeks**

Very high responder rate to TP-03: **96%** of patients improved at least 1 collarette grade; **89%** achieved a clinically meaningful cure

Efficacy goal
1° collarette cure rate,
2° mite eradication,
2° redness + collarette cure rate

Safety goal
Well-tolerated safety profile

NDA, New Drug Application.
Data on file. Tarsus Pharmaceuticals Incorporated; 2022

55

COLLARETTE SCALE USED TO DETERMINE SEVERITY OF *DEMODEX* BLEPHARITIS

Grades 2-4 Indicate Clinically Significant Disease

GRADE 4
- >2/3 of lashes on lid with collarettes
- Approximately 150 collarettes/lid*

GRADE 3
- Between 1/3 to 2/3 of lashes on lid with collarettes
- Approximately 100 collarettes/lid*

GRADE 2
- Between 10 collarettes to 1/3 of lashes on lid with collarettes
- Approximately 50 collarettes/lid*

Chances of *Demodex* infestation increase with >10 collarettes/lid[3,4]

AVERAGE BASELINE = GRADE 3 FOR SATURN-1 and SATURN-2 STUDIES[1,2]

Grades 0-1 Indicate Clinically Meaningful Cure

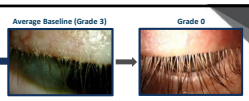
GRADE 1
- 3 to 10 collarettes on the lashes

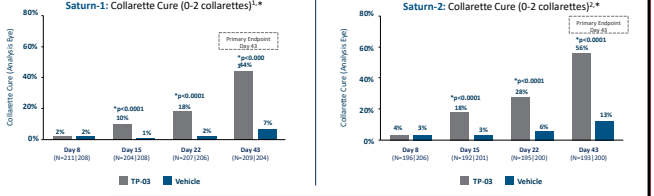
GRADE 0
- 0 to 2 collarettes on the lashes
- FDA primary endpoint: Complete cure of collarettes

*For an upper eyelid with 150 eyelashes (number of eyelashes on the upper eyelid may vary from 90 to 160). Photos are images taken of patients in Saturn-1 with the corresponding collarette grade.
FDA, Food and Drug Administration.
1. Yeu E et al. *Cornea.* 2022; In Press. 2. Data on file. Tarsus Pharmaceuticals, Incorporated; 2022. 3. Gonzalez-Salinas R et al. *J Ocul Pharmacol Ther.* 2021;37(8):479-484. 4. Gao YY et al. *Invest Ophthalmol Vis Sci.* 2005;46(9):3088-3094

56

PRIMARY ENDPOINT OF COLLARETTE CURE (≤2 COLLARETTES) ACHIEVED



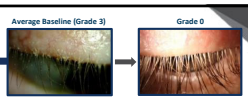


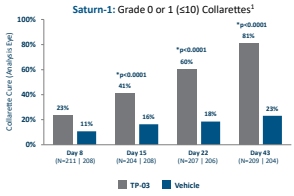
Regulatory endpoint of statistically significant Complete Collarette Cure in TP-03 group compared to vehicle observed by Week 2

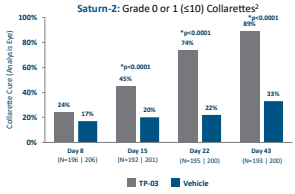
*The primary efficacy endpoint was the proportion of patients achieving collarette cure (0-2 collarettes on the eyelid) as compared to the vehicle control, at Day 43.
1. Yeu E et al. *Cornea.* 2022; In Press. 2. Data on file. Tarsus Pharmaceuticals, Inc.2022.

57

CLINICALLY MEANINGFUL COLLARETTE REDUCTION (≤10 COLLARETTES) ACHIEVED







Statistically significant clinically meaningful Collarette Reduction in TP-03 group compared to vehicle observed by Week 2

1. Yeu E et al. *Cornea.* 2022; In Press. 2. Data on file. Tarsus Pharmaceuticals, Inc. 2022.

58

OCULAR ADVERSE EVENT SUMMARY

- Overall there were low rates of ocular AEs across both studies

Saturn-1: Treatment-Related Ocular AE Rates ≥1%[1]

	TP-03 (n=212)	Vehicle (n=209)
Instillation Site Pain/Burning/Stinging	25 (11.8%)	16 (7.7%)
Instillation Site Pruritus	3 (1.4%)	7 (3.3%)
Visual Acuity Reduced	3 (1.4%)	5 (2.4%)
Eye Pain	3 (1.4%)	2 (1.0%)
Eye Discharge	3 (1.4%)	1 (0.5%)
Dry Eye	0	1 (0.5%)
AE Severity	All mild	1 moderate All others mild

Saturn-2: Treatment-Related Ocular AE Rates ≥1%[2]

	TP-03 (n=203)	Vehicle (n=209)
Instillation Site Pain/Burning/Stinging	16 (7.9%)	14 (6.7%)
Instillation Site Pruritus	1 (0.5%)	1 (0.5%)
Visual Acuity Reduced	1 (0.5%)	3 (1.4%)
Eye Pain	1 (0.5%)	0
Eye Discharge	1 (0.5%)	0
Dry Eye	3 (1.5%)	1 (0.5%)
AE Severity	2 moderate All others mild	1 moderate All others mild

All AEs were mild or moderate

AE, adverse event.
1. Yeu E et al. *Cornea.* 2022; In Press. 2. Data on file. Tarsus Pharmaceuticals Incorporated; 2022.

59

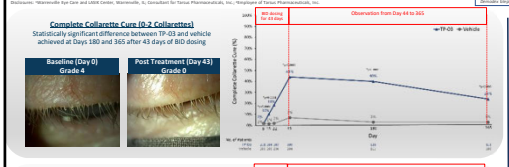
Extended Observational Safety Trial to Evaluate the Long-Term Safety of Lotilaner Ophthalmic Solution, 0.25% for the Treatment of *Demodex* Blepharitis

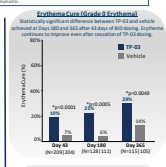
Saturn-1 Extension Study

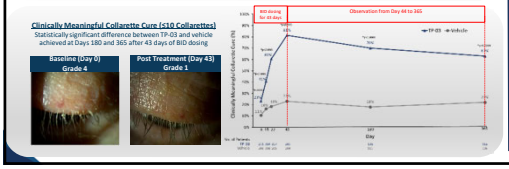
Lisa Nijm, MD, JD[1]; Mark Holdbrook[2]; Stephanie Baba, OD[1]; Saturn-1 Extension Study Group[†]
Disclosures: [1]Bienville Eye Care and LSEM Center, Mooresville, IL. Consultant for Tarsus Pharmaceuticals, Inc. [2]Employee of Tarsus Pharmaceuticals, Inc.

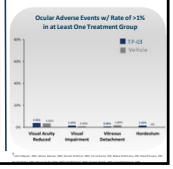
Study Overview

Demodex blepharitis is present in the majority of canine patients; however, there are no FDA-approved therapeutics for this condition. The results of this extension study, a continuation from the Phase 2b/3 randomized, controlled, double-masked study of 425 subjects at 15 US sites demonstrated the long-term safety (Day 180 and 365) following acute administration (BID for 43 days) of lotilaner ophthalmic solution, 0.25% (Tarsus Pharmaceuticals) for the treatment of *Demodex* blepharitis.









60

Xdemvy thoughts

- Will it have to be used every year?
- Will adjunct therapy be needed?
- Why not just do IPL?
- Is this approved?

61

The Dry Eye Scene

Tell Me About Something New… Please!!

62

The newest thing in Dry Eye- Miebo

- Miebo (Perfluorohexyloctane) – B&L
- Indicated for treatment of evaporative Dry Eye Disease
- Mimics critical function of meibum
- QID (for how long)?

63

Miebo – Mechanism of Action

- Meibo is a perfluorocarbon
- A portion of the molecule anchors in the lipid layer
- The other portion rises away from the lipid layer
- Creates a low surface tension which allows for rapid spread across surface
- Forms an anti-evaporative layer
- Inhibits tear film evaporation for up to 6 hrs

64

Miebo – unique characteristics

- 100% drug (active ingredient)
- No vehicle
- No preservative
- No water
- Very small drop (11 mcl)
- Safe for long term usage
- Indicated for evaporative dry eye
- Reduces blink friction
- Improves tear film homeostasis
- Gets into glands and stays for 24 hrs
- Reduces evaporation by 28% (even more w/ more meibum)

How do you diagnose evaporative dry eye?

65

So where does Miebo fit into our dry eye protocol?

66

The New Dry Eye Hot Topic- Neurotrophic Keratitis!

- What is NK?
- How does it look clinically?
- What are the symptoms?
- How do you diagnose NK?
- How do you treat NK?

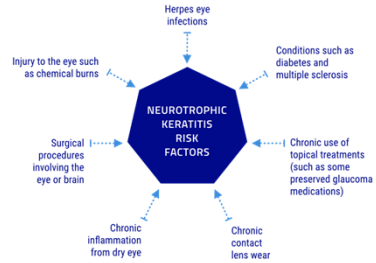
67

Neurotrophic keratitis

- Degenerative Corneal Disease Characterized by:
  - Impaired corneal healing
  - Decreased Corneal sensitivity
  - Spontaneous epithelial breakdown
- There is usually a predisposing cause, but impaired trigeminal nerve innervation is the root
- Symptoms may be absent- certainly underwhelming in comparison to their corneal appearance

68

Neurotrophic Keratitis



69

NK symptoms

- Dryness
- Reduced Blink
- Blurred Vision
- Photophobia
- Px may be asymptomatic

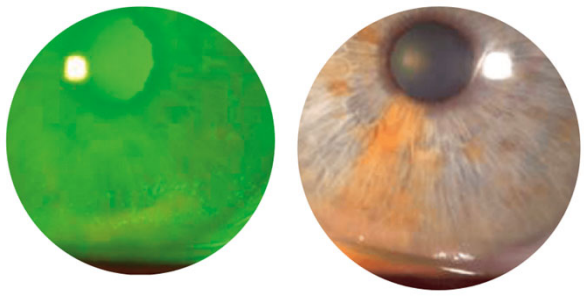
70

NK- Diagnosis

- History
- Slit lamp exam – corneal appearance
- Corneal sensitivity testing

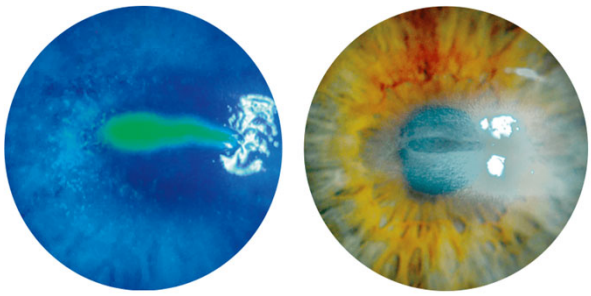
71

NK Stage 1



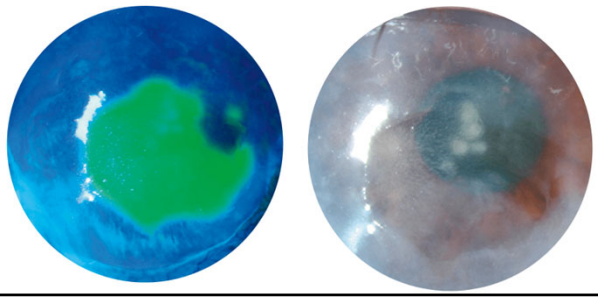
72

NK – Stage 2



73

NK- Stage 3

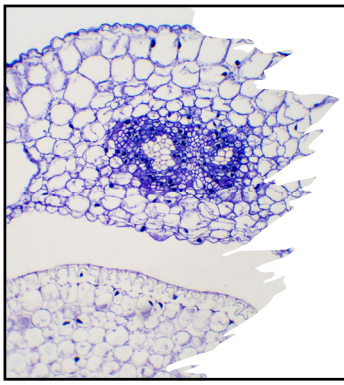


74

NK Treatment

- BCL?
- Autologous serum
- Cryopreserved amniotic membrane
- Oxervate!!!

75



Oxervate- cenergemin (Dompe)

- Synthetic rhNGF
- Structurally identical to endogenous NGF
- Improves corneal nerve function(innervation)
- Promotes tear secretion
- Fosters epithelial cell growth

76

What exactly is Neurotrophic Growth Factor?

- NGF induces corneal healing and has the potential to restore sensitivity and may modulate inflammatory reactions in the eye
- NGF has the potential to increase tear production and conjunctival goblet cell density and promote nerve regeneration after mechanical corneal nerve injury
- NGF activates TrkA and p75 Neurotrophin receptor expressed on corneal epithelial cells and sensory neurons and may stimulate mucin release and goblet cell differentiation
- NGF is a naturally occurring neurotrophin is responsible for differentiation, growth and maintenance of neurons
- Neuromediators from corneal nerves provide trophic support to ocular surface tissues (particularly epithelial cells and keratocytes that: Stimulate wound healing and maintain anatomic integrity.
- Epithelial cells release neurotrophins, neuropeptides and growth factors (e.g. NGF) from epithelial cells and keratocytes that mediate nerve fiber survival, differentiation and maturation.
- Corneal nerves stimulate blinking and tear production.
- Tears contain growth factors and nutrients that stimulate epithelial cells

77

Oxervate

1 DROP 6X/DAY

DELIVERED OVER A 12 HR PERIOD

8 WEEK TREATMENT DURATION

78

Oxervate data

- 8 week study period- compared to placebo
- 72% achieved complete K healing
  - Absence of NaFl stain at lesion site
  - No persistent staining on rest of corneal surface
- 80% remained completely healed at 12 mths
- Most common AE – Eye pain (12%)

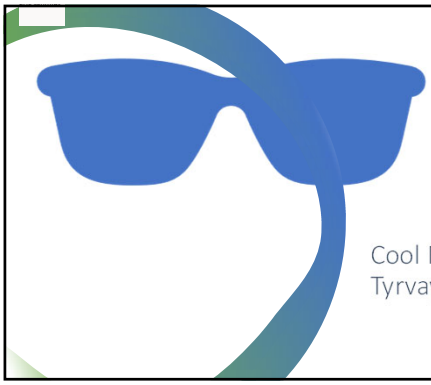
79

A lesser New Thing

- Tyrvaya (varenicline nasal spray 0.03mg)
  - Viatris
- Works by activating trigeminal parasympathetic pathway via the nose
- Increases basal tear production
- Dosage- 1 sqn each nostril Q12H
- Unique Home Delivery System

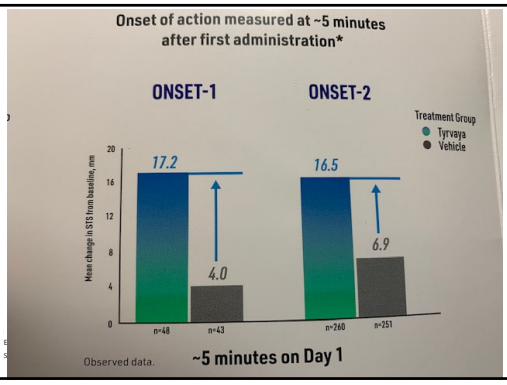
80

81

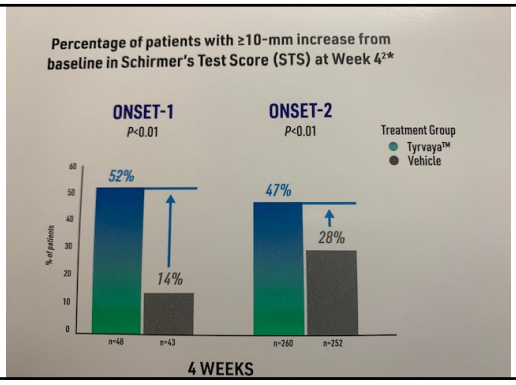


Cool Man- But Does Tyrvaya Really Work?

82



83



84

85

Tyrvaya- Adverse Effects

- Sneezing -82%!!!
- Cough – 16%
- Throat Irritation – 13%
- Nose Irritation – 8%

86

So Tell Me Oh Great One- What Do We Really Think About Tyrvaya?

87

Steroid Update

88

Steroid Update

- Lotemax SM (loteprednol 0.38%)– B & L
  - SM = submicron particles
  - Enhances dissolution of drug into tear film
  - This effectively doubles penetration through cornea when compared to LE Gel
  - Lotemax gel and Lotemax are 0,5% concentration

89

Lotemax SM

- Emulsion so no shaking required
  - Btw why is that a big deal?
- Very low concentration of BAK (.003%)
- Does not blur vision as much as LE Gel
- Quickly turns into a viscous liquid

- Steroid response rate?
  - 2 out of 409 had 10mm or higher rise in IOP after 18 days

90

Inveltys (Kala/Alcon Pharmaceuticals)

- Loteprednol etabonate 1%
- Indication – Tx of post-op inflammation and ocular pain
- BID dosing
- Nanoparticle technology allows for increased penetration and increased drug concentration into target tissue
- Doesn't bind (as much) to mucin

91

Inveltys

Time to Zero inflammation	Time to Zero pain	0.5% IOP rise
• 24% at Day 8 • 50% at Day 15	• 43% at Day 4 • 69% at Day 15	

92

So what do we make of Inveltys?

Would you change your post-op regimen?

What about for Ocular Surface inflammation?

How expensive is it??

93

Eyesuvis- loteprednol etabonate (0.25%) Alcon

- Clinical Indication- Short term therapy for the signs and symptoms of dry eye
- It is a suspension, so…
- Dosage – BID x 2 weeks
  - Does not need to be tapered
- For the treatment of Dry Eye "Flares" –
  - Is a dry eye flare really a thing?
- So is it just another Alrex?

94

Eyesuvis – Clinical Studies

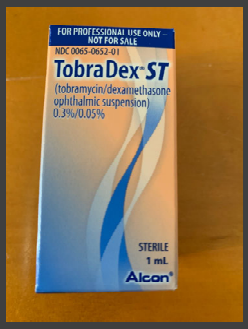
- Clinically Significant improvement in both:
  - signs (ocular discomfort)
  - Symptoms (redness)
- In Dry Eye patients at both:
  - Hour 4
  - Day 14
- 0% Steroid responders in study
- MPP technology increases penetration through tears and contact time on conjunctival surface

95

YES THERE IS A COUPON FOR EYESUVIS!!!

96

Tobradex ST (Eyevance)



97

Who Doesn't Like Tobradex??

So what's new with TD ST??
- Half the steroid concentration
- Less steroid response
- Indicated for "steroid-responsive inflammatory conditions"

What's not new with TD ST??
- Still a suspension so it still needs to be shaken
- It should still be tapered

What's with the ST??
- Increases retention time on ocular surface
- Enhances bactericidal activity
- Equal to TD in anti-inflammatory ability

Is there any reason to RX "regular " Tobradex any longer?

98

1 More Topic –
Autologous Serum

99

Autologous Serum – The How

- More aptly called Eye-Platelet Rich Plasma (EPRP)
- Eyedrops created from patient's own blood
- Blood is drawn and spun down
- WBC and RBC are all removed by centrifugation; platelets and growth factors remain
- Plasma is placed in sterile eyedrop bottle

100

Autologous Serum – The Why

- Autologous plasma is rich in platelets and growth factors
- Growth factors enhance proliferation and wound healing
- Effective on hard and soft tissues
- Growth factors restore damaged ocular surface by inducing mesenchymal and epithelial cells to migrate and proliferate

101

Autologous Serum – The What For?

- Severe Dry Eye
- Corneal Ulcers (especially if dormant)
- Non-healing epithelial defects
- LASIK complications
- Chronic Dystrophies (EBMD)

102

Kojima study – Am J Ophthalmol, 2005

- E-PRP for Dry Eye
- Conclusion- Autologous plasma is superior to conventional treatment for improving ocular surface health and subjective comfort
- E-PRP improved tear stability and vital staining scores (RB)

103

Autologous Serum Studies

- Alio – Ophthalmology 2007
- E-PRP improved symptoms – photophobia, pain, inflammation
- E-PRP facilitated re-epithelialization
- E-PRP promoted wound healing
- Improved VA
- ".. In the majority of the patients in the study."

104

Autologous Serum What Does it Really Mean?

- Autologous Serum brings growth factors directly to compromised eye.
- Diseased eye is not getting nutrients to help healing
- Diseased eye is undergoing chronic tissue breakdown
- E-PRP breaks that cycle

105

Autologous Serum – Clinical Questions

- What is the dosage?
- Where should it be kept?
- When should it be Rx'd?
- How Can I actually Acquire It???

106

Welcome Regener-Eyes

- Regener-Eyes – The first topical biologic eye drop
- Multiple Allogenic Proteins Paracrine Signaling (MAPPS)
  - Derived from mesenchymal tissue
- Active ingredients are cytokines, chemokines and growth factors
- But you don't have to get a blood draw!

107

Regener-Eyes- MOA

- Blocks Inflammation
- Promotes Tissue Healing
- Signals Human Growth Factors
- Recruits more chemokines (which further promote wound healing).
- Immunomodulators

108

Regener-Eyes

- Dosage – 1 drop up to 4x/day
- 2 strengths- Professional and Lite
  - Professional strength must be refrigerated
- Preservative Free
- Lasts for 90 days once opened
- Unique delivery model

109

Macular Degeneration Update

- A Very Hot Topic!
- We have 1 approved drug for Geographic Atrophy
- We will have another one approved in August
- What Do They Do?
- How Are They Different?

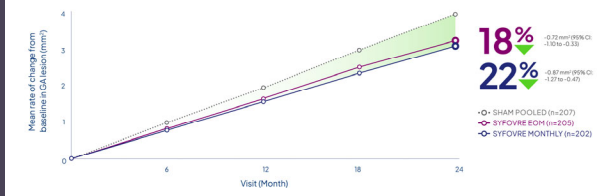
110

Syfovre (pegcetacoplan inj) - Apellis

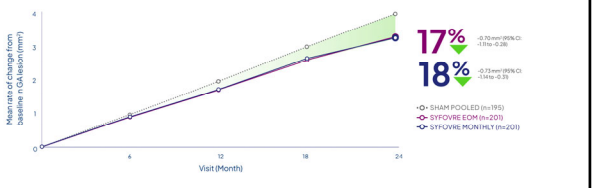
- Has been shown to decrease the rate of lesion growth in Geographic Atrophy
- When does it work best?
- Is it worth it?

111

- Reduction in Lesion Growth Rate



112



- REDUCTION IN LESION GROWTH RATE WITH SYFOVRE VS SHAM POOLED[1,2*]

113

OAKS + DERBY

114

- SYFOVRE reduced GA lesion growth rate vs sham pooled in lesions with and without subfoveal involvement through Month 24[4]
-
- Combined

115

Most Common Adverse Events

- Monthly vs Every Other Month vs Sham
- Discomfort – 13% , 10%, 11%
- SRNVM - 12%, 7%, 3%
- Floaters - 10%, 7%, 1%
- Inflammation 4%, 2%, <1%

116

GA drug #2-Iveric Bio

- Not yet approved
- PDUFA date early August
- Same delivery schedule as Syfovre
- ? Can it actually improve VA?

117

So What Does This All Mean for ODs and GA?

118

Geographic Atrophy

- WE NEED TO PAY CLOSER ATTENTION TO GEOGRAPHIC ATROPHY
- MORE FREQUENT OCT SCANS
- MORE FREQUENT FOLLOW UP
- KNOW WHAT THE CRITERIA FOR REFERRAL AND TREATMENT IS
- CHOOSE YOUR RETINAL SURGEON WISELY

119

Presbyopia Drop Landscape

July 2023

120

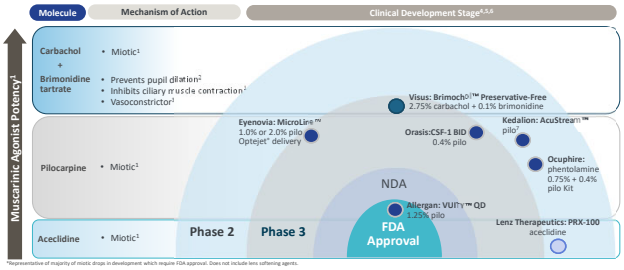
Pharmacologic Treatments for Presbyopia Are Emerging, With Miotic Drops Occupying the Majority of Development

Topical Drops in Development/Approved	Active Ingredient(s)	Mechanism of Action
VUITY™ (Allergan) – FDA Approved *(BID study ongoing)*	Pilocarpine	Miotic
BRIMOCHOL™ (Visus Therapeutics)	Carbachol + brimonidine tartrate	Carbachol: Miotic Brimonidine tartrate: Prevents pupil dilation, inhibits contraction of ciliary muscle, increases bioavailability of carbachol[1,2], prevents redness[3]
CSF-1 (Orasis)	Pilocarpine	Miotic
PRX-100/Liquid Vision (LENZ Therapeutics)	Aceclidine	Miotic
MicroLine/OpteJet™ (Eyenovia)	Pilocarpine	Miotic
AcuStream™ (Kedalion)	Pilocarpine	Miotic
Nyxol® and Pilocarpine Combination Kit (Ocuphire)	Phentolamine mesylate and pilocarpine	Miotic (both pilocarpine and phentolamine mesylate products) Vasodilates small muscles (phentolamine mesylate product)[4]

1. Suzuki et al. Ocular and Systemic Pharmacokinetics of Brimonidine and Timolol After Topical Administration in Rabbits: Comparison Between Fixed-Combination and Single Drugs. *Ophthalmol Ther* (2020) 9:115–125. 2. Allergan patent application (Pub. No.: US 2018/0078560 A1). 3. LUMIFY® Product Insert www.fda.gov accessed 9/24/2020. 4. Pepose. Phentolamine Mesylate Ophthalmic Solution Provides Long Lasting Pupil Modulation And Improves Visual Acuity, ARVO 2020 Abstract: #3864450.

121

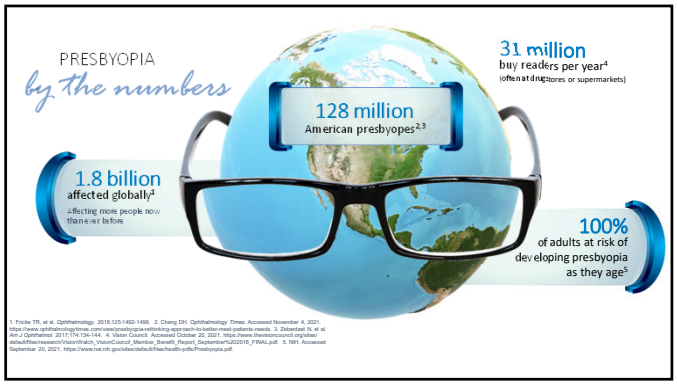
Presbyopia-Correcting Miotic Drop Landscape By Stage of Development & Muscarinic Agonist Potency*



*Representative of majority of miotic drops in development which require FDA approval. Does not include lens softening agents.

1. A. Grzybowski MD, PhD et al. A Review of Pharmacological Presbyopia Treatments. *Asia-Pacific Journal of Ophthalmology* Philadelphia, PA. nih.gov (June 4, 2020). 2 . J.E MacDonald et al. Effect of brimonidine tartrate-ophthalmic solution 0.2% on pupil size in normal eyes under different luminance conditions. *J Cataract Refract Surg.* 2020 Apr;27(4):560-3. 3. R.E Kerbundy, PhD. Cardiovascular Pharmacology. January 2021. 4. August 2021 Clinicaltrials.gov. 5 OIS Presbyopia Innovation Showcase, January 28, 2021. 6. ASCRS Eyecelerator, July 2021. 7. UNSW Australia pilocarpine via AcuStream Presbyopia Recruitment Advertisement, concentration unknown.

122



1. Fricke TR, et al. *Ophthalmology.* 2018;125:1492-1499. 2. Chang DH. *Ophthalmology Times.* Accessed November 4, 2021. https://www.ophthalmologytimes.com/view/presbyopia-rethinking-approach-to-better-meet-patients-needs. 3. Zebardast N, et al. *Am J Ophthalmol.* 2017;174:134-144. 4. Vision Council. Accessed October 20, 2021. https://www.thevisioncouncil.org/sites/default/files/research/VisionWatch_VisionCouncil_Member_Benefit_Report_September%202016_FINAL.pdf. 5. NIH. Accessed September 20, 2021. https://www.nei.nih.gov/sites/default/files/health-pdfs/Presbyopia.pdf.

123

New Therapeutics for Clinical Practice

124

- SMELLS LIKE OPPORTUNITY TO ME!!!!
  - But who is our target?
  - Do the drops really work?
  - Will they have a negative impact on m optical?
  - What about for CL wearers?
  - What about for Pseudophakes?
  - Are they safe?
  - Do we have any new information?

125