What's New In the Treatment of MGD and Blepharitis?

COPE#76761-TD

Walt Whitley, OD, MBA, FAAO

Dry Eye in the Desert

Woo University

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

- Aerie: Consultant, Speaker
- Alcon: Consultant, Speaker
- Allergan: Consultant
- Astareal: Consultant
- Bausch and Lomb: Consultant
- Bruder: Consultant
- CollaborativeEye: Co-Chief Medical Editor
- Dompe: Consultant
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- Tarsus Pharmaceuticals: Consultant
- TearLab Corporation: Consultant
- ThermaMEDx: Consultant
- Visus Pharmaceuticals: Consultant

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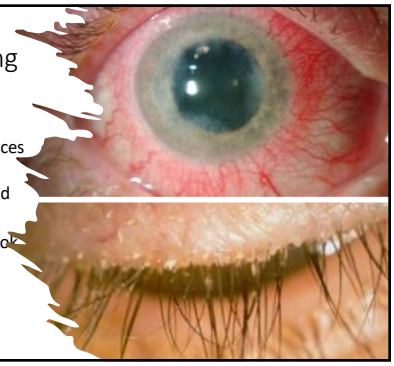
4 Steps to Beating Blepharitis

- Understand the differences among presentation
- Know the prevalence and who is affected
- Listen to patients and look for this disease
- Treat and manage appropriately



https://www.optometrytimes.com/view/4-steps-beating-blepharitis

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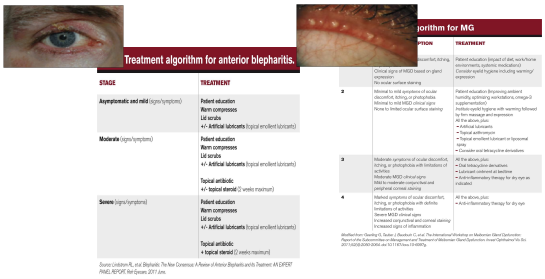
So Where Were We a Decade Ago?



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TFOS DEWS II Definition

*"Dry eye is a multifactorial disease of the ocular surface characterized by a **loss of homeostasis** of the tear film, and accompanied by **ocular symptoms**, in which tear film **instability** and **hyperosmolarity**, ocular surface **inflammation** and damage, and **neurosensory abnormalities** play etiological roles."*

Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK, Liu Z, Nelson JD, Nichols JJ, Tsubota K, Stapleton F. TFOS DEWS II Definition and Classification Report. Ocul Surf. 2017 Jul;15(3):276-283. doi: 10.1016/j.jtos.2017.05.008. Epub 2017 Jul 20. PMID: 28736335.

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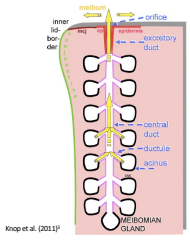
The Meibomian Glands



Knop et al. (2011)[3]

- Modified sebaceous glands located superficially in the tarsal plate[2,3,6]
  - Should sit just anterior to muco-cutaneous junction in healthy patient
  - 25-40 in upper eyelid
  - 20-30 in lower eyelid
- Each gland is comprised of[2,3,6]:
  - Meibocytes (secretory cells)
  - Lateral ductules
  - Central duct
  - Terminal excretory duct at the lid margin
- Densely innervated[2,3,6]
  - Function related to hormones, growth factors, neurotransmitters, etc.

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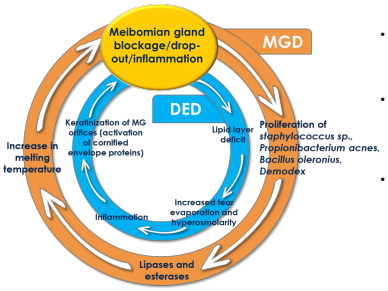
Mechanism of disease



- Lipids from meibomian glands necessary for ocular surface health and integrity[1]
- Blocked meibomian glands lead to gland dilation, atrophy, low secretion, gland dropout and compromised tear film[1]
- **Meibomian gland health is integral to a healthy tearfilm[2]**

1. Boudouin C et al, "Revisiting the vicious circle of dry eye disease: a focus on the pathophysiology of meibomian gland dysfunction". Br J Ophthalmol, Vol 100(3), pp 300–306. 2. Dry eye management: targeting the ocular surface microenvironment. Int J Mol Sci. 2017; 18: E1398

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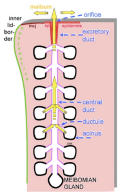
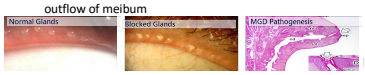
Keratinization may be present in multiple places in the Meibomian gland: Gland Orifice

- Hyperkeratinization at the gland orifice is a leading pathogenesis of MGD[1]
  - Keratin formation is a natural process
  - Keratin is produced and sheds at physiological rates to confer its protective role while not accumulating in excess
  - At the gland orifice on the lid margin:
  - Hyperproliferation may produce excess keratin (directly related to an oil producing gland)
  - Terminal Duct Obstruction: Stress at the lid margin results in excess keratinization and excess keratin may block the glands and restricts outflow of meibum





Knop E, Knop N, Millar T, Obata H, Sullivan DA. The International workshop on meibomian gland dysfunction: report of the subcommittee on anatomy, physiology, and pathophysiology of the meibomian gland. Invest Ophthalmol Vis Sci. 2011;52(6):1938-78.

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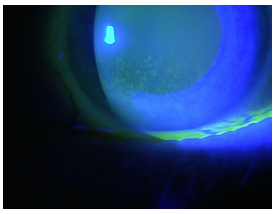
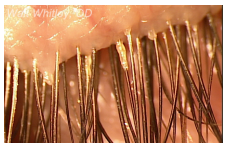
Patient Education is Key!!





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Why Is Patient Education Important?

- Impact of DED/MGD on quality of life and surgical outcomes
- Improves interprofessional collaboration and communication
- Manage patient expectations
- Treatments are self-administered; patients need to stay motivated to adhere to treatment
  - Seeing objective measurements and images are helpful (eg, meibomian gland dropout, topography readings) and helps patients adhere to treatment
  - Having a written plan is important
    - Patients forget
    - Regimens are complicated
    - COVID-19/telehealth

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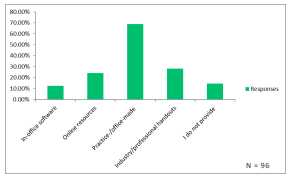
Poll Results: What resources do you use for patient education on DED management?

- In-office patient engagement software (13%)
- Recommendations for online resources (24%)
- Practice-/Office-made handouts (67%)
- Industry or professional society handouts (28%)
- I do not provide or recommend educational materials on DED management (13%)



> 1 response allowed

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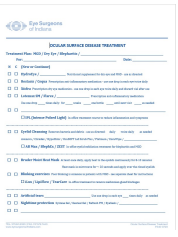
Patient Education Samples

Courtesy of Walter O. Whitley, OD, MBA, FAAO, and Virginia Eye Consultants



Courtesy of Damon Dierker, OD, and Eye Surgeons of Indiana

Courtesy of Eric D. Donnenfeld, MD, and Ophthalmic Consultants of Long Island and Connecticut

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OSD Treatment Strategies in 2022

- Lubricants
  - Tears (emulsions, solutions), gels, ointments, sustained-release formulation
  - Ingredients
    - Hyaluronic acid, Carboxymethylcellulose (CMC), Lipid-based
- Nutrition
  - Oral essential fatty acids
  - Vitamin A ointment

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OSD Treatment Strategies in 2022: Lid Margin Disease Management

- Warm compress and lid massage
  - Difficult to maintain adequate temperature; poor compliance
- Lid scrubs
  - Commercial soap scrubs
  - Tea tree oil in *Demodex* mite infestation[1]
- In-office lid margin cleansing and meibomian gland expression for anterior blepharitis and posterior blepharitis
  - Motorized/mechanical devices[2]
  - Thermal and thermal pulsation[3]
  - Intraductal probing[4]
  - Intense pulsed light[5]
  - Radiofrequency

1. Gao YY, et al. *Cornea*. 2007;26(2):136-143; 2. Korb DR, Blackie CA. *Cornea*. 2013;32(12):1554-15
3. Lane SS, et al. *Cornea*. 2012;31(4):396-404; 4. Maskin SL. *Cornea*. 2010;29(10):1145-1152;
5. Craig JP, et al. *Invest Ophthalmol Vis Sci*. 2015;56(3):1965-1970.

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OSD Treatment Strategies in 2022

- Anti-inflammatory agents
  - Topical corticosteroids
  - Topical cyclosporine A emulsion (CSA) 0.05% and 0.09%
  - Topical lifitegrast, 5%
  - Oral tetracyclines or macrolides
  - Topical azithromycin
- Amniotic membrane products: anti-inflammatory and promote wound healing
- Neurostimulation
  - Intranasal neurostimulation - pharmacologic
  - Extranasal neurostimulation

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Dry Eye Homework

Lid Hygiene

Heat Masks / Kits

Neurostimulation

Combined Lid Hygiene and Heat Mask

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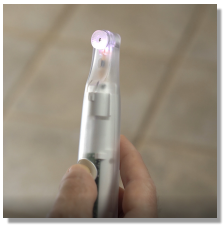
At Home Mechanical Eyelid Device

- The Starter Kit includes; rechargeable cordless handpiece, charger plug and cord, and 30 to 180-day supply of Daily Disposable Soft Tips
- A new sterile Soft Tip is attached to the handpiece daily
- A small amount of lubricating gel or cleaner is applied to the edge of the Soft Tip to enhance comfort.
- The Soft Tip oscillates gently over closed eyelids for 30 seconds per eye per day



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JOURNAL OF DRY EYE DISEASE

Original Article

EFFICACY OF SELF-ADMINISTRATION OF A PERSONAL MECHANICAL EYELID DEVICE FOR THE TREATMENT OF DRY EYE DISEASE, BLEPHARITIS, AND MEIBOMIAN GLAND DISEASE

David Schanzlin MD[1], John Olkowski MD[2], John Coble OD[3], Wendy Gross OD[1], Michael Dash OD[2]
[1]Gordon-Schanzlin New Vision Institute, San Diego, CA
[2]EyeSight Hawaii Vision Institute, Honolulu, HI
[3]Eyecare of Greenville, Greenville, TX

Corresponding Author: jolkowski1@gmail.com

Submitted: November 3, 2019. Accepted: December 17, 2019. Published: January X, 2020.

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TA[redacted] – Efficacy Endpoint Results

	PRE-TREATMENT	POST-TREATMENT	P-VALUE
OSDI	54.2 ± 19.5	26.7 ± 18.4	$P < 0.001$
TOT (mOsm/L)	315 ± 15.7	306 ± 13.9	$P = 0.002$
TBUT (seconds)	4.8 ± 1.7	7.9 ± 4.1	$P < 0.001$
MGS	8.9 ± 5.1	7.0 ± 5.9	$P = 0.01$
MGYLS	8.7 ± 6.2	15.8 ± 6.9	$P = 0.002$
SOSS	2.7 ± 2.1	1.4 ± 1.5	$P = 0.002$

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NuSight Medical ®

An Evaluation of the Effect a Manual Eyelid Cleaning Device has on **Donor Cornea Epithelium after Direct Application**

John Olkowski MD*; EyeSight Hawaii Vision Institute, Honolulu, HI
Reprints: John Olkowski, MD, EyeSight Hawaii Vision Institute, 650 Iwilei Road, Suite 210, Honolulu, HI 96817 (e-mail: jolkowski1@gmail.com)
J. Olkowski has financial interest in NuSight Medical.
Key words: Dry eye disease, blepharitis, Meibomian gland disease

NuLids has ZERO REPORTABLE ADVERSE EVENTS
After 750,000+ patient home treatments over 3+ years

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INTRODUCING [redacted]

A new MGD treatment advancing patient care

Instant, Precise Heat & Pre-Moistened Cleaning Pad in One Convenient, Easy to Use Therapy

- Class I Med Device: United States
- Class IIA Med Device: Europe

THERMAMEDX

2/24/22 - CONFIDENTIAL DO NOT SHARE OR FORWARD

- ✓ Sterile, Precise Daily, Moist Heat to Help Manage the Underlying Issues Associated with MGD
- ✓ Designed to Improve Patient Compliance by Eliminating the Need for Multiple Products

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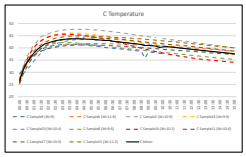
THE SCIENCE OF PRECISE HEAT
Innovation & Technology

EVERTEARS HEAT PROFILE

In Vitro Temperature Profile



In Vitro Maximum Temperature

	IR	C
N	10	10
Mean	42.2	43.9
Median	41.9	43.9
Std. Deviation	3.3	2.2
Minimum	38.4	41.3
Maximum	49.6	47.7
25%	39.1	41.7
50%	41.9	43.9
75%	44.1	45.7

TEMPERATURE RANGE IMPLICATION
≥ 40oC up to 12:00min

2/24/22 - CONFIDENTIAL DO NOT SHARE OR FORWARD

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THIS SIMPLE, AFFORDABLE TREATMENT
Will change the quality of life for MGD patients

ACTIVATE HEAT

< 20 secs to activate heat for compress up to 10 mins

GENTLE CLEANING

~ 2 to 3 mins per eye with gentle cleaning of lids

2/24/22 - CONFIDENTIAL DO NOT SHARE OR FORWARD

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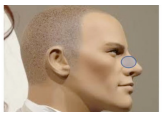
FDA Label

INDICATION FOR USE

The [redacted] Neurostimulator™ is an electromechanical nerve stimulator device, indicated for temporary use (up to 30 days) to increase acute tear production during vibratory stimulation of the external nasal nerve in adults, under prescription of an eyecare provider.



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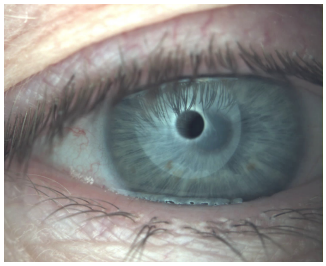
Immediate TEAR Response and Meibum Secretion



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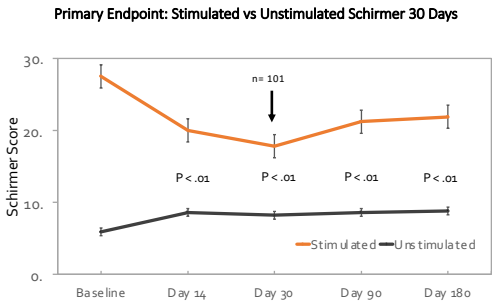

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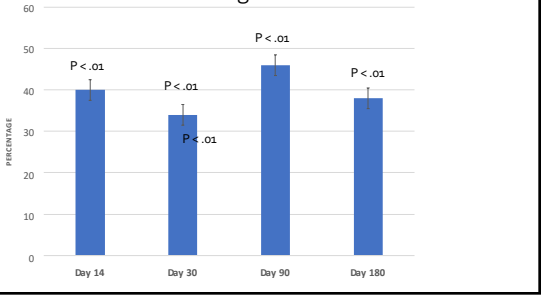

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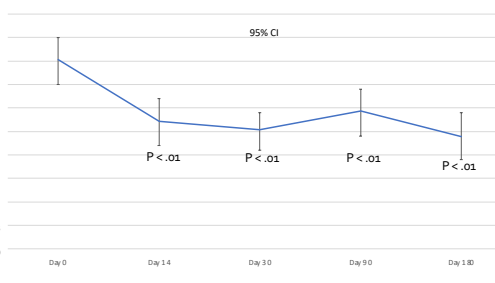

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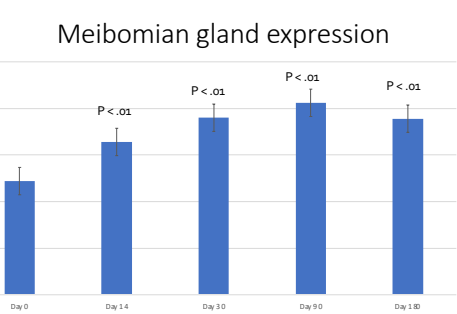

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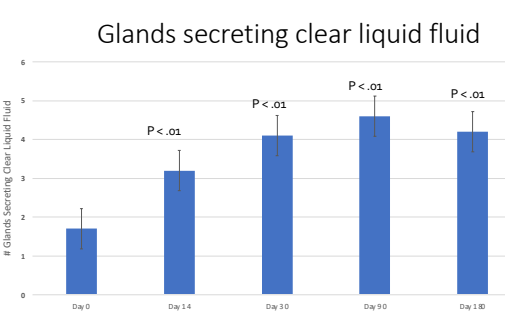

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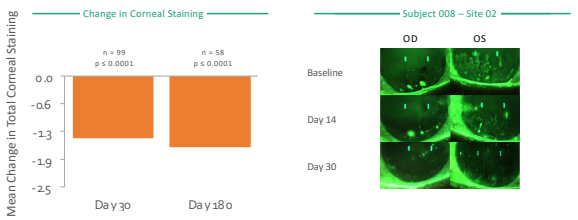
Corneal Staining



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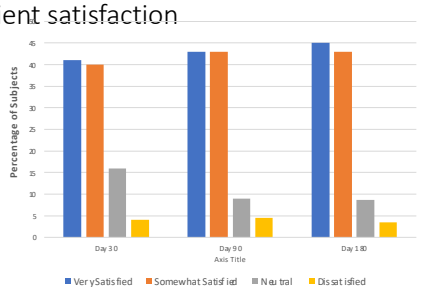
Patient satisfaction



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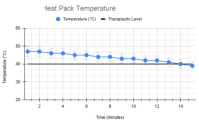
The First Open-Eye Warm Compress

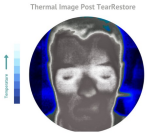
Effective & Consistent Heat

TearRestore supplies therapeutic heat (>40C) for a minimum of ten minutes every use. This ensures patients and doctors an effective treatment every time.



Unique Convenience & Natural Expression

TearRestore's design utilizes anatomical norms to target the eyelids while avoiding the globe. This permits the user to see and blink throughout treatment, resulting in improved compliance and natural meibomian gland expression.



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How Do You Simplify OTC Treatments?

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In-Office Procedures are Growing!!

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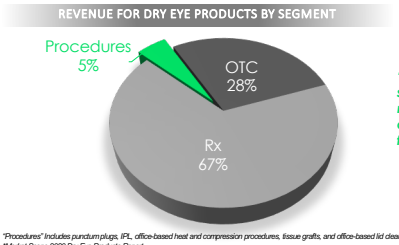
PROCEDURES CURRENTLY REPRESENT 5% OF US DRY EYE REVENUE*



"The overall procedure segment of the dry eye market will grow rapidly during our five-year forecast period"

– Market Scope

"Procedures" includes punctum plugs, IPL, office-based heat and compression procedures, tissue grafts, and office-based lid cleansings.
"Market Scope 2020 Dry Eye Products Report

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Vector Thermal Pulsation

Long-Term (3 Year) Effects of a Single Thermal Pulsation System Treatment on Meibomian Gland Function and Dry Eye Symptoms

Jack V. Greiner †

Affiliations + expand

PMID: 29222895 DOI: 10.1097/ICL.0000000000001166

Abstract

Purpose: The present study examined the long-term (3 years) effects of a single (12 min) thermal pulsation system (TPS) treatment on symptomatic patients with evaporative dry eye disease (DED) secondary to meibomian gland dysfunction (MGD).

Methods: In this prospective, cohort, observational, single-center study design, signs (meibomian gland secretion [MGS] scores and tear film breakup time [TBUT]) and symptoms (Ocular Surface Disease Index [OSDI] and Standard Patient Evaluation of Eye Dryness [SPEED] questionnaires) were determined in 20 patients (40 eyes) with MGD and dry eye symptoms at baseline (BL), 1 month, and 3 years post-TPS treatment using LipiFlow.

Results: Meibomian gland secretion scores increased from BL (4.5±0.8) to 1 month (12.0±1.1, P≤0.001). Improvement persisted at 3 years (18.4±1.4) relative to BL (P≤0.001). Meibomian gland secretion scores in all regions of the lower eyelid were improved over BL at 1 month (nasal [P≤0.001], central [P≤0.001], temporal [P≤0.01]) and 3 years (nasal [P≤0.001], central [P≤0.001], temporal [P=0.005]). TBUT increased from BL (4.7±4.4) to 1 month (7.8±3.4, P≤0.05) but was not significantly different than BL at 3 years (4.5±3.6, P>0.05). The OSDI scores decreased from BL (26.0±4.6) to 1 month (14.7±4.3, P≤0.001) but returned to BL levels at 3 years (22.5±5.4, P>0.05). The SPEED scores decreased from BL (13.4±1.0) to 1 month (6.5±1.3, P≤0.001), and this improvement persisted at 3 years (9.5±1.6, P≤0.001).

Conclusions: Thermal pulsation may be a uniquely efficacious treatment option for DED secondary to MGD in that a single 12-min procedure is associated with significant improvement in MGS and SPEED scores for up to 3 years.

- Results
  - Meibomian gland secretion scores increased from BL (4.5±0.8) to 1 month (12.0±1.1, P≤0.001). Improvement persisted at 3 years (18.4±1.4) relative to BL (P≤0.001).
  - OSDI scores decreased from BL (26.0±4.6) to 1 month (14.7±4.3, P≤0.001) but returned to BL levels at 3 years (22.5±5.4, P>0.05).
  - SPEED scores decreased from BL (13.4±1.0) to 1 month (6.5±1.3, P≤0.001), and this improvement persisted at 3 years (9.5±1.6, P≤0.001).

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A Novel, Targeted, Open Eye, Thermal Therapy and Meibomian Gland Clearance in the Treatment of Dye Eye:

A Randomized Controlled Investigator masked Trial (OLYMPIA)

Jennifer M. Loh, MD, ABO; William B. Trattler, MD, ABO; Kavita P. Dhamdhere, MD, PhD; Marc R. Bloomenstein, OD; John A. Hovanesian, MD; Mitchell A. Jackson, MD, ABO; Bobby Saenz, OD

Presented by Jennifer M. Loh, MD, ABO; ASCRS May 16, 2020

Primary Endpoint: Tear Film Break-Up Time (TBUT)

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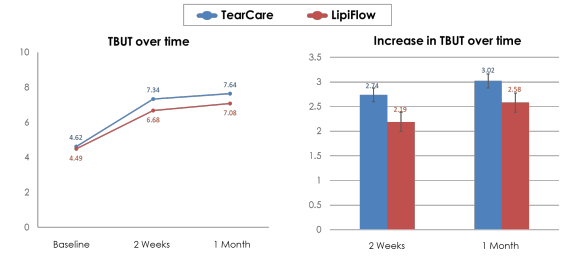
Primary Endpoint: Tear Film Break-Up Time (TBUT)



- Statistically significant increase (p<0.0001)in mean TBUT in both groups at all f/u time points
- **TearCare is non-inferior to LipiFlow**

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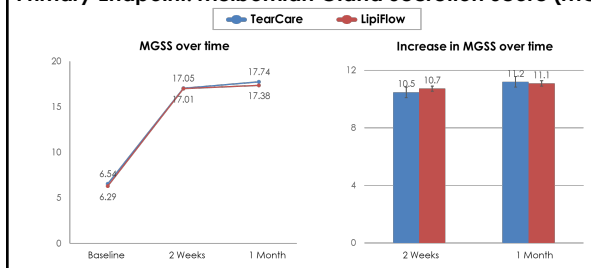
Primary Endpoint: Meibomian Gland Secretion Score (MGSS)



- Statistically significant increase (p<0.0001)in mean MGSS in both groups at all f/u time points
- **TearCare is non-inferior to LipiFlow**

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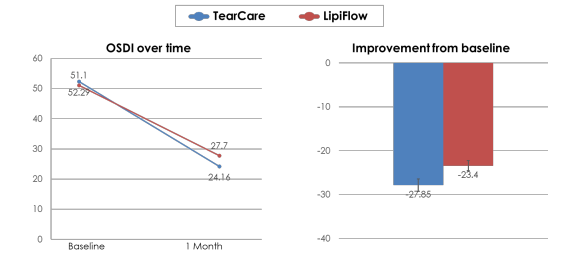
Secondary Endpoint: Ocular Surface Disease Index (OSDI)



Statistically significant improvement (p<0.0001) in mean OSDI score compared to baseline

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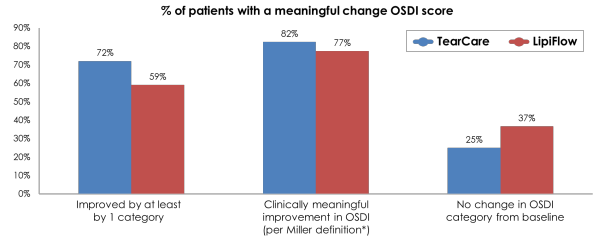
A greater proportion of TearCare patients showed meaningful symptom relief*



72% of TearCare vs 59% for LipiFlow subjects improved by at least 1 ***OSDI*** category

*per Miller definition

42

Conclusions

TearCare successfully met non-inferiority objective v. LipiFlow

- ✓ 82% of TearCare subjects had clinically meaningful improvements in OSDI
- ✓ TBUT, MGSS, Conjunctival and Corneal staining, Glands Yielding any liquid, Glands Yielding clear liquid
- ✓ OSDI, SANDE, Eye Dryness Score

A **greater proportion** of patients in **TearCare** group showed clinically **meaningful symptomatic relief** compared to LipiFlow group

- ✓ 72% of TearCare vs 59% for LipiFlow subjects improved by at least 1 OSDI category
- ✓ 22% less use of lubricant drops throughout the study follow up in TearCare group

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In-Office MGD Treatment

Handheld iLux® device

- Magnifier allows the user to **view the eyelid margin**
- **Warms** the eyelid tissue within a therapeutic target range to melt the meibum blocking the orifices, then **applies compression** to express the melted meibum through the orifices
- Amount of heat and pressure is under **direct control of the user**

iLux® Smart Tip

- Sterile, **single-patient-use** disposable tip
- **Inner and outer pads** are covered with a soft, biocompatible silicone material
- Contains **precision temperature sensors** that continually monitor inner and outer eyelid temperature and ensure therapeutic heat levels during treatment

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Clin Ophthalmol. 2020; 14: 405–418. PMCID: PMC7024784
Published online 2020 Feb 12. doi: 10.2147/OPTH.S234668 PMID: 32103887

Comparison of the iLUX and the LipiFlow for the Treatment of Meibomian Gland Dysfunction and Symptoms: A Randomized Clinical Trial

Joseph Tauber,[1] James Owen,[2] Marc Bloomenstein,[3] John Hovanesian,[4] and Mark A Bullimore[5]

› Author information › Article notes › Copyright and License information Disclaimer

Abstract Go to: ⓘ

Results

Both devices significantly improved effectiveness outcomes, with no differences between the two devices. At the 4-week visit, mean MGS, TBUT, and OSDI scores improved at least 16.9 ± 11.5, 2.6 ± 3.2 s, and 28.0 ± 22.8, respectively, across treatment groups and treated eyes. Four device/procedure-related events occurred in the iLUX group, compared with none in the LipiFlow group, but there were no device-related adverse events that involved changes in lid margins, eyelids, or lash integrity. Corneal staining, intraocular pressure, and visual acuity did not differ in the two groups.

Conclusion

Both treatments produced significant improvements in meibomian gland function and symptoms. For all effectiveness measures, there were no statistically significant differences between the two treatments.

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Does Not Cause Excessive Heating of the Eye

- An open-label safety study of iLux® found **no sign of excessive heating** of the cornea, outer eyelid, or surrounding surface[1]*
- Standard optometric assessments of the cornea and subjects' vision demonstrated **no corneal damage and minimal impact on vision**[1]*

Comparison of pre- and post-heating temperature readings (n=30 eyes)[1]*

Tissue Site	Pre-heating temperature (°C)	Post-heating temperature (°C)	Change in temperature (°C)
Corneal	Maximum: 36.9 Mean: 36.0 ± 0.6	Maximum: 38.8 Mean: 37.7 ± 0.5	+1.8
Outer eyelid	Maximum: 37.4 Mean 36.5 ± 0.5	Maximum: 40.6 Mean: 38.5 ± 0.8	+3.2
Surrounding surface	Maximum: 37.6 Mean: 36.8 ± 0.5	Maximum: 39.7 Mean: 38.2 ± 0.7	+2.1

* Heating performed in the medial-nasal and medial-temporal zones in the upper and lower eyelids of each eye for 90 seconds in each zone

Reference: 1. Hardten DR, Karpecki PM, Owen J. Safety parameters of a handheld infrared heating and compression device for management of Meibomian gland dysfunction. Presented at the ASCRS-ASOA Annual Meeting, April 13-17, 2018. Washington, D.C.

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Systane® iLux® MGD Thermal Pulsation System

1 Week / 1 Month Study Design[1]

Stud ective:
o assess changes in meibomian gland function and evaporative dry eye symptoms after treatment with Systane® iLux®

Stud ign:
non-randomized, open-label, multisite trial

Subj
30 subjects

- **Primary endpoints**
  MGS and TBUT
- **Secondary endpoint**
  SPEED score and OSDI symptom scores

Assessed pre-treatment, and at 1 week and 1 month post-treatment

MGD, meibomian gland dysfunction.
Reference: 1. Alcon data on file, 2011.

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Systane® iLux® MGD Thermal Pulsation System Delivered Significant Improvements in 1 Week in a Clinical Study[1]

Significant improvements seen
1 week after treatment with Systane® iLux®

Meibomian Gland Score ($P<0.0001$)	Tear break-up time ($P<0.0001$)	SPEED Questionnaire ($P<0.0001$)	OSDI Score ($P=0.0003$)
315% improvement	**71%** improvement	**55%** improvement	**58%** improvement
Medial, temporal, nasal regions all improved		Improvement in all 8 sub-scores	

All improvements **maintained at 1 month**

In a prospective, open-label, multicenter study of patients ≥18 years with MGD (n=30).
*8-item questionnaire that scores patient experience of dry eye before and after a treatment. Total SPEED score calculated through sum of all 8 items; total score value can vary from 0–28, with higher score indicating worse experience of dry eye.
MGD, meibomian gland dysfunction; OSDI, Ocular Surface Disease Index; SPEED, Standard Patient Evaluation of Eye Dryness.
Reference: 1. Alcon data on file, 2011.

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Safety of Systane® iLux® in 1 Week / 1 Month Study

In the non-randomized clinical study of the Systane® iLux® MGD Thermal Pulsation System[1]

- **No adverse events or serious adverse events reported**[1]
- Pain scores increased post treatment, but **returned to pre-treatment values one day post treatment**[1]
- **1 week post treatment pain scores were significantly lower than pretreatment values** (both eyes, *P*<0.0001)[1]

- **No clinically significant changes in IOP** occurred immediately post-treatment or throughout follow-up[1]
- **No change in lid abnormalities** associated with treatment[1]

in a prospective, open-label, multicenter study of patients ≥18 years with MGD (n=30).

MGD, meibomian gland dysfunction; OSDI, Ocular Surface Disease Index.

Reference: 1. Alcon data on file, 2011.

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Phase 4, 12-Month Follow-Up Study of Systane® iLux®[1,2]

Study Objective:
compare meibomian gland function and impact of dry eye symptoms on
of follow-up after treatment with Systane® iLux® and Lipiflow^

Study Design:
prospective, randomized, parallel group, investigator-masked, multicenter, noninferiority study

Subjects:
236 subjects with MGD

- **Endpoints**
  - MGS
  - IDEEL-SB
  - TBUT

Assessed at baseline, 2 weeks and 1, 3, 6, 9, and 12 months

2021 Annual Meeting; May 1-7; online

Alcon 50

50

Noninferiority Over 12 Months* With Systane® iLux®[1]

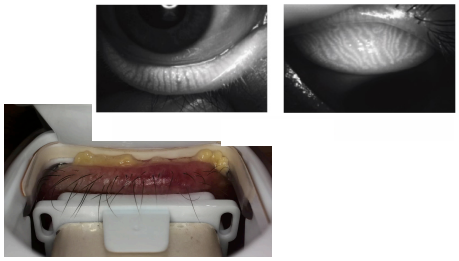
MGS

IDEEL-SB Score

-7; online meeting.

Alcon 51

51



52

Intense Pulsed Light

- The specific mechanism of action is not well understood but is believed to be partially due to the thermal heating of the meibum coupled with the therapeutic effects of treating superficial telangiectasia

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Clinical Ophthalmology

Dovepress

CLINICAL TRIAL REPORT

Prospective evaluation of intense pulsed light and meibomian gland expression efficacy on relieving signs and symptoms of dry eye disease due to meibomian gland dysfunction

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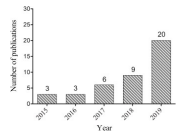
Analysis of Cytokine Levels in Tears and Clinical Correlations After Intense Pulsed Light Treating Meibomian Gland Dysfunction

Results:

- All of the inflammatory markers declined in value compared to baselines.
- IL-17A and IL-6 showed statistically significant decreases compared to sham treatment at each measured time point.
- PGE2 showed statistically significant decreases compared to sham at week 12.
- Results showed that the expressions of IL-17A and IL-6 correlated well with ocular surface parameters of the lower eyelid before IPL.

55

Intense Pulsed Light Therapy In The Treatment Of Meibomian Gland Dysfunction: Current Perspectives



https://www.sciencedirect.com/science/article/pii/S1542012420300999

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Dry Eye and More!!

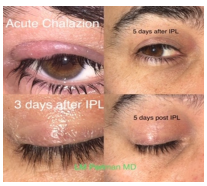

Photo Courtesy of Laura Perriman, MD aka "The Dry Eye Master"

57

Dry Eye and More!!

Photo Courtesy of Laura Perriman, MD aka "The Dry Eye Master"

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Radiofrequency

- FDA cleared (K130689) and indicated for use in dermatological and general surgical procedures for electrocoagulation and hemostasis; creation of lesions in nerve tissue.
- Associated with improving skin laxity and wrinkle reduction using a **Radio Frequency Thermistor Heating Device**

Slide Courtesy of Drs. Christensen and Hauser

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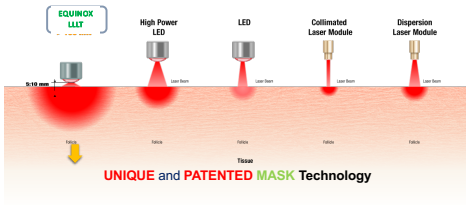
LLLT & LED Technology



60

Photobiostimulation

Red light is absorbed in the cellular mitochondria and stimulates ATP production leading to an increased cellular action and enhanced cell vitality.

The 633 nm emitted light is potentially absorbed by fibroblasts, with a subsequent increase in the speed and efficiency of neo-collagen synthesis. *Turnover of aged collagen and elastin fibers* results from light stimulation of metalloproteinases (MMP's).

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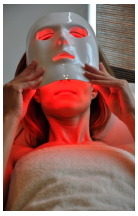
Advanced Technology



- Computer Driven
- Select Level of MGD 1-4 = Calculates correct Energy and Time (15min Max)
- Apply Comfortable Mask
- Both Eyes/Lids Treated Simultaneously
- Automated Treatment Starts & Stops with Countdown Timer
- Visible Results Possible for Patient after 1st Treatment

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Like With Lasers – Color Matters

BLUE LIGHT:
Purification action. The blue light is recognized to be the ideal wavelength to solicit porphyrins to obtain a bacteriostatic effect with a consequent **elimination of bacteria**

YELLOW LIGHT:
Specific action on the lymphatic system. The yellow light stimulates cell's metabolism promoting a ***de-toxifying action*** to relief swelling conditions.

RED LIGHT:
Stimulates production of collagen and elastin. Through the **EQUINOX LLLT®** technology, the red light is absorbed by mitochondria and **stimulates ATP increasing cellular action, enhancing it's activity**.

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Ophthalmology Times
CUTTING-EDGE ADVANCEMENTS

OphthalmologyTimes › Ophthalmology › Drug Therapy - Ophthalmology

Red light technology increases tear break-up time in dry eye patients

More than 90% of subjects report improvement in symptoms in study

November 15, 2015 | By Lynda Charters, Rolando Toyos MD

Take-home message: Treatment with red light technology resulted in a significant improvement in the tear break-up time in the vast majority of patients. This may be a future light treatment for the improvement of dry eye disease in patients with meibomian gland dysfunction.

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Treatments For More Conditions

- Resolution of Recalcitrant Chalazia

- 1 Treatment >>>> Resolution of 46% Of Eyes
- 2 Treatments >>>> Resolution of 92% Of Eyes

WITH STANDARD RED EQUINOX LLLT MASK

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Treatments For More Conditions

- Rosacea

← **STEP 1 – BLUE MASK**
The BLUE wavelength stimulates porphyrins to create a **natural anti-bacterial action**

STEP 2 – RED MASK →
The RED wavelength stimulates mitochondria that produces ATP. It increases and **improves cellular activity to works on inflammation**

66

66

Treatments For More Conditions

- Demodex

← **STEP 1 – BLUE MASK**
The BLUE wavelength stimulates porphyrins to create a **natural anti-bacterial action**

STEP 2 – RED MASK →
The RED wavelength stimulates mitochondria that produces ATP. It increases and improves **cellular activity to works on inflammation**

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With So Many Treatment Options for MGD, How Do you Choose?

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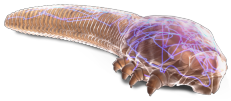
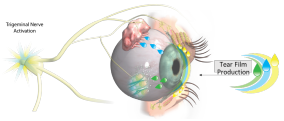
Future Innovations in MGD / Blepharitis





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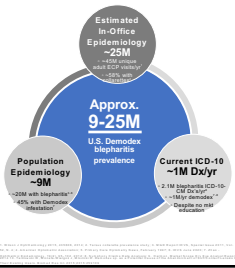
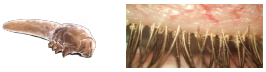
Blepharitis is a Large and Underserved Market in Eye Care





Largely Underdiagnosed, Education Needed	~ 58% of all patients in the eye clinic have collarettes[2] but current impression of only 10-15% of blepharitis cases
Significant head start on Diagnosis	2.1M ICD-10 Blepharitis Dx's/yr[6]
Blepharitis Routinely Causes	Eyelids to become red, irritated and itchy, with debris on the eyelashes[3]
Blepharitis Can Lead To	Blurring of vision, missing or misdirected eyelashes, and inflammation of other eye tissue, particularly the cornea[4]
Blepharitis and Surgery	Important factor for maximizing surgical outcomes: 67% of cataract patients have Demodex blepharitis[5]
Contact Lens Drop-out	#1 reason people discontinue contact lens wear is discomfort. Studies have shown a direct correlation between Demodex blepharitis and CL intolerance [5,20]
Prescription Treatment	None

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Demodex is an Underlying Cause of Blepharitis

2 Species of Mites Contribute to Blepharitis

- *Demodex folliculorum*: eyelash follicles
- *Demodex brevis*: meibomian glands in eyelid

***Demodex* Implicated in 45% of Blepharitis Cases**

- Meta-analysis of 11 studies and 4,741 pts[1]

Demodex Overgrowth Causes Disease in 3 Ways

1. Mechanical: overcrowding, obstruction, eyelash loss, irritation
2. Chemical: digestive enzymes and waste
3. Bacterial: inflammation from surface/gut bacteria

Zhao - Ophthalmic Epidemiology, 19(2), 95–102, 2012

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Collarettes Are Pathognomonic Sign of Demodex Infestation

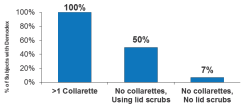
Collarettes Are Composed of Mite Waste Products and Eggs[1]

- Regurgitated undigested material combined with epithelial cells, keratin, and mite eggs
- Contain digestive enzymes, which cause irritation

% of Subjects with Demodex

Easily and Rapidly Diagnosed with Standard Eye Exam

- Demodex mites found on 100% of lashes with collarettes[2]
- Collarettes found in ~ 58% eye care patients[3]

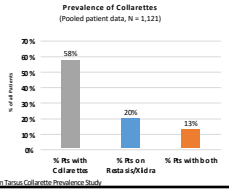


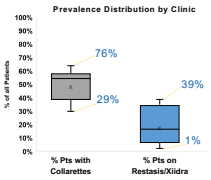
1. Fromstein 2018
2. Gao et al., Invest Ophth and Vis Sci, September 2005, Vol. 46, No. 3089-3094.

72

Half of All Patients Entering Clinic have Collarettes

- Since Demodex is newly appreciated as a cause of blepharitis, Tarsus performed the first-ever Demodex blepharitis in-clinic prevalence study
- Methods: [redacted] consecutive patient seen by the clinic is evaluated for
  1. Presence of collarettes (the pathognomonic sign and key diagnostic for Demodex blepharitis)
  2. Whether they have an active Rx for dry eye (Restasis® or Xiidra®)
- N = 1,121 consecutive patients, 8 clinics (MDs and ODs, geographically diverse)





Note: Data from Tarsus Collarette Prevalence Study

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Conventional Treatment Methods Are Not Effective in Managing Demodex Blepharitis

- Cannot be killed by Baby shampoo (common lid hygiene)
- Cannot be killed by 10% Propidone iodine (surgical scrub)
- Cannot be killed by 75% alcohol
- Cannot be killed by Macrolides such as erythromycin (antibiotic)
- Cannot be killed by Metronidazole (for Rosacea treatment)
- Cannot be killed by 4% Pilocarpine (for lice treatment)
- Killed dose-dependently by Tea Tree Oil (TTO), derived from Melaleuca alternifolia

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Tea Tree Oil

- Compounding Pharmacy
- 50% Solution of Tea Tree Oil
- 20% Solution of Tea Tree Ointment
- Tea Tree Shampoo
- Tea Tree Soap
- Numerous OTC treatments

75

TP-03 is a Novel Drug Designed to Treat Demodex Blepharitis by Eradicating Mites and Collarettes[1]

Product Form	Multi-dose eye drop solution bottle, preserved
Targeted Use	Treatment of Demodex blepharitis
MOA	Paralysis and death of Demodex mites
Diagnosis	Collarettes identified in standard eye examination
Dosing	BID* for 6 weeks
Efficacy Goal	1º collarette cure, 2º mite eradication, 2º redness + collarette cure
Safety Goal	Well-tolerated safety profile

1. TP-03 Product profile based on Tarsus-1 Trial Design

***Not FDA Approved

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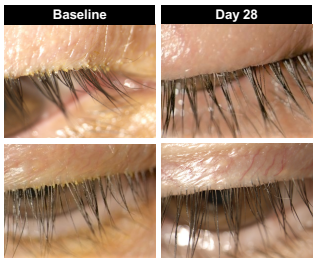
Cure of Collarettes with BID Use of TP-03

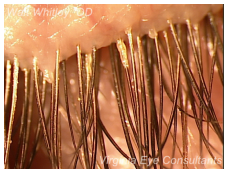


***Not FDA Approved

77

TP-03 for Demodex Blepharitis

- Single-arm, open-label study that evaluated the safety and efficacy of TP-03 in 15 participants with Demodex Blepharitis over 28 days
- **Collarette Score:** The mean grade showed statistically significant improvement from baseline to day 14 and had a 2-grade improvement overall on a 4-point scale
- **Mite Eradication:** The average mites/lash showed statistically significant improvement from baseline to day 14 and had a 10-fold improvement from baseline
- No treatment-related adverse events were reported



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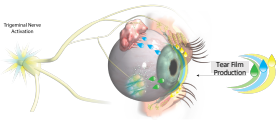
The Parasympathetic Nervous System (PNS) Is a Critical Regulator of the Lacrimal Functional Unit (LFU) and a Healthy Tear Film

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.

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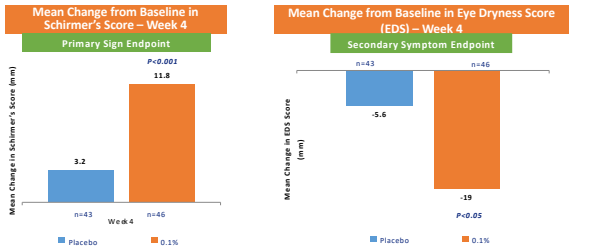
OC-01 Demonstrated Statistically Significant Improvement in Signs and Symptoms of Dry Eye Disease (DED)

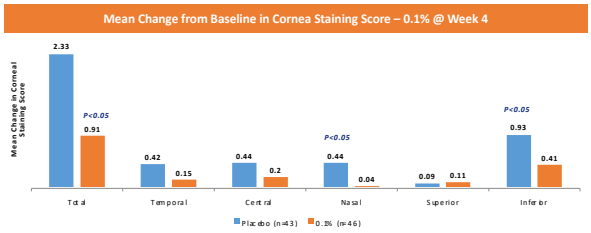
Note: The CAE was **not** used for this measurement.



ITT-observed population
ANCOVA, Least Squares means

80

OC-01 Demonstrated Significant Difference from Placebo in Mean Change in Corneal Staining in Total, Nasal and Inferior Regions



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OC-01 is Well Tolerated with Zero Ocular Side Effects

Adverse Events Potentially Related to OC-01 >5% of subjects

Occurred at least once after any installation	OC-01 (0.1%) (n=48)	Placebo (n=43)
Sneeze	38 (79)	0
Cough	6 (13)	0
Throat irritation	7 (15)	0
Instillation site irritation	8 (17)	0
Pharynx dysaesthesia	4 (8)	0

- All events transient and self-limiting immediately following administration
- All events mild (94%) or moderate (4%) in severity. No severe events.
- **No ocular adverse events**; Side effects consistent with that of any nasal spray (sneeze, cough, irritation)

On Track for Initiating Phase 3 in 2019

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ONSET-2 Top Line Results

- Primary endpoint: Statistically significant improvement in percentage of subjects gaining ≥ 10mm on Schirmer's Score in both doses tested 0.6 mg/ml and 1.2 mg/ml) as compared to control (p<0.0001). Consistent outcome with ONSET-1
- Statistically significant improvement in mean change in Schirmer's Score in both doses tested as compared to control (p<0.0001). Consistent outcome with ONSET-1
- Eye Dryness Score measured in the normal clinic environment demonstrated SS improvement as compared to control in the 1.2 mg/ml dose group at Week 4 (p<0.009) and as early as Week 2 (p=0.002)
- Most common AE was sneeze, which was predominantly transient and mild

***NDA filed 3/2/21

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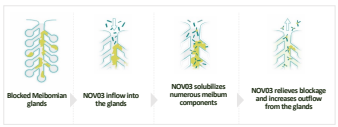
NOV03 Perfluorohexyloctane - Dual Mode of Action



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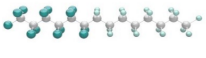
NOV03 Perfluorohexyloctane



	Water-based Technologies	NOV03
Drop Size	~ 40–50µL (Blink reflex activated)	< 12 µL (Blink reflex not activated)
Drug Residual Time	Brief 3–5 min	Long ~ 240 min
Spreading	High surface tension hinders spreading	Fast spreading Film forming properties
Other features	Usually Preserved	Preservative free No vision blurring

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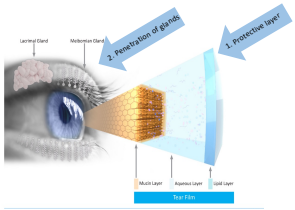
NOV03 – Dual Mode of Action

Phase 3: ESSENCE-2
0.1% CsA in EyeSol

Water-free

Preservative Free

Penetration of meibomian glands and potentially solubilizing blocked Meibum



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NOV03 has been Evaluated in Several Small Clinical Studies in the EU

- Steven P, Scherer D, Krösser S, Beckert M, Cursiefen C, Kaercher T. Semifluorinated alkane eye drops for treatment of dry eye disease—A prospective, multicenter noninterventional study. J Ocular Pharmacol Ther 2015;31(8):498-503. https://pubmed.ncbi.nlm.nih.gov/26296040/
- Steven P, Augustin AJ, Geerling G, et al. Semifluorinated alkane eye drops for treatment of dry eye disease due to meibomian gland disease. J Ocul Pharmacol Ther 2017;33(9):678-685. https://pubmed.ncbi.nlm.nih.gov/28922088/
- Eberwein P, Krösser S, Steven P. Semifluorinated alkane eye drops in chronic ocular graftversus-host disease: A prospective, multicenter, noninterventional study. Ophthal Res. 2020;63:50-58.
- Garhofer G, Schmidl D, Werkmeister RM, et al. Influence of perfhluorohexyloctane containing eye drops on tear film thickness in patients with mild to moderate dry eye disease. Invest Ophthalmol Vis Sci. 2018;59(9):941. https://iovs.arvojournals.org/article.aspx?articleid=2689663&resultClick=1

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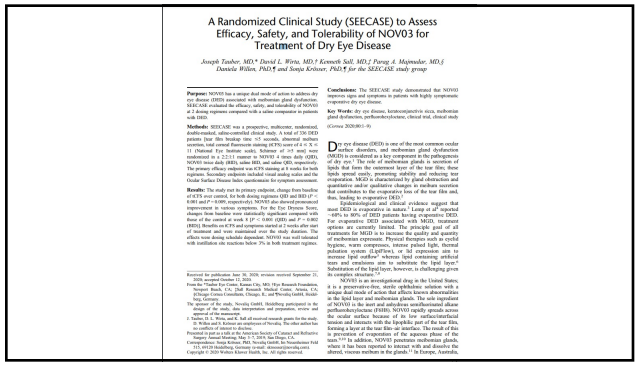

A Randomized Clinical Study (SEECASE) to Assess Efficacy, Safety, and Tolerability of NOV03 for Treatment of Dry Eye Disease

Joseph Tauber, MD, David L. Wirta, MD,† Kenneth Sall, MD,‡ Parag A. Majmudar, MD,§ Daniela Willen, PhD,¶ and Sonja Krösser, PhD,¶ for the SEECASE study group*

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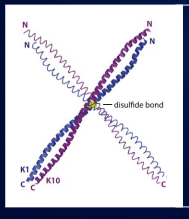
TARGETING ABERRANT KERATIN

Unblocking Glands and Disruption of Keratin Plaques Within Meibum Matrix



Keratins are helical structural proteins that make up hair, nails, and skin

Extremely resilient and insoluble

Disulfide bond cross linking hardens structures to give strength and durability

Thermal denaturing
Disulfide bonds are comparatively strong and require considerable thermal energy to break, >144 °C

Chemical denaturing
Readily achieved chemically with a mild disulfide bond disrupting agent, i.e. keratolytic

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WHAT ARE KERATOLYTICS?

Agents that soften and shed the skin epithelium or horny outer layer of skin through the process of breaking down keratin

- Similar to the lid margin, secretory gland hyperkeratinization plays an important role in various skin disorders
- Comedonal lesions in acne are inspissated hair follicles, filled with corneocytes, sebum, and other debris
- Keratolytic treatments are used to shed dead corneocytes, loosen the sebum plug, and prevent the formation of inflammatory papules and pustules

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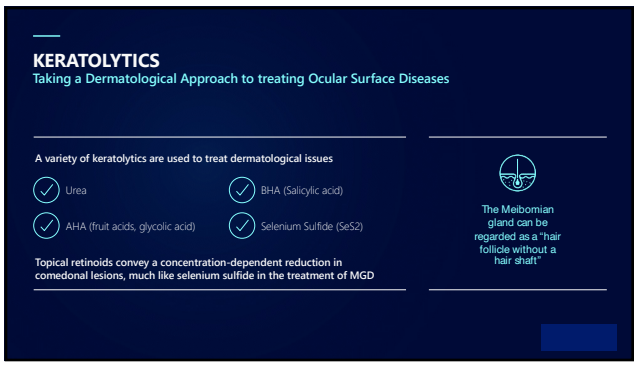

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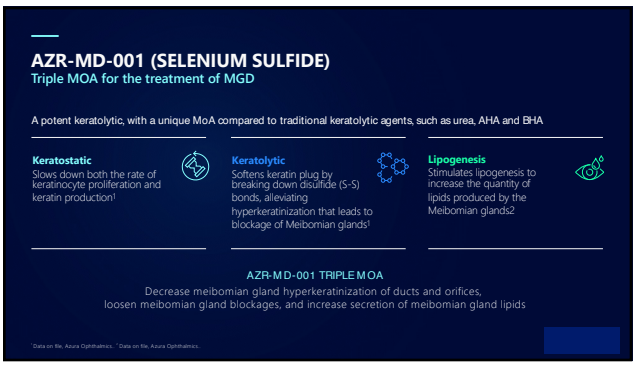

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Conclusions

- Exciting era for treatments in lid margin disease
- Only non-obvious if you don't look and express
- Identify and treat the root cause of dry eye disease
- Consider current and innovative treatments for MGD / Blepharitis

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Questions??

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