

New Treatments for DED

José M. Benítez-del-Castillo

Professor of Ophthalmology

Universidad Complutense de Madrid

Hospital Clínico San Carlos

Clínica Rementería, Madrid

Spain

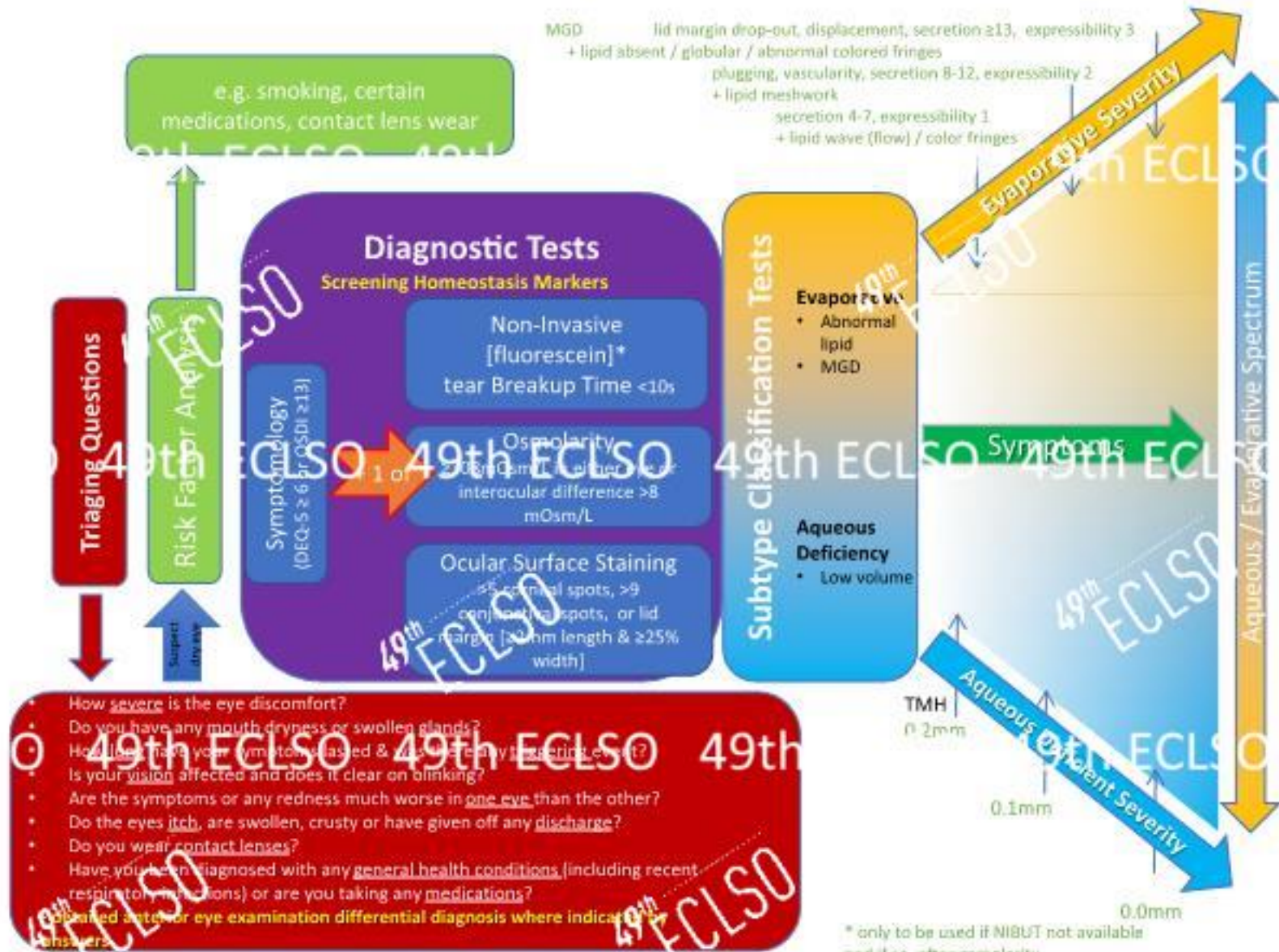


Financial Disclosure

- Aicon
- Allergan
- Santen
- Brill
- Angelini
- Esteve
- J & J
- Avizor
- Dompé
- B+L
- Novartis
- Visufarma
- Thea
- Abbvie
- Oculus
- Farmamix

TFOS DEWS II revised 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.”



* only to be used if NIBUT not available and if so, after osmolarity



Contents lists available at ScienceDirect

The Ocular Surface

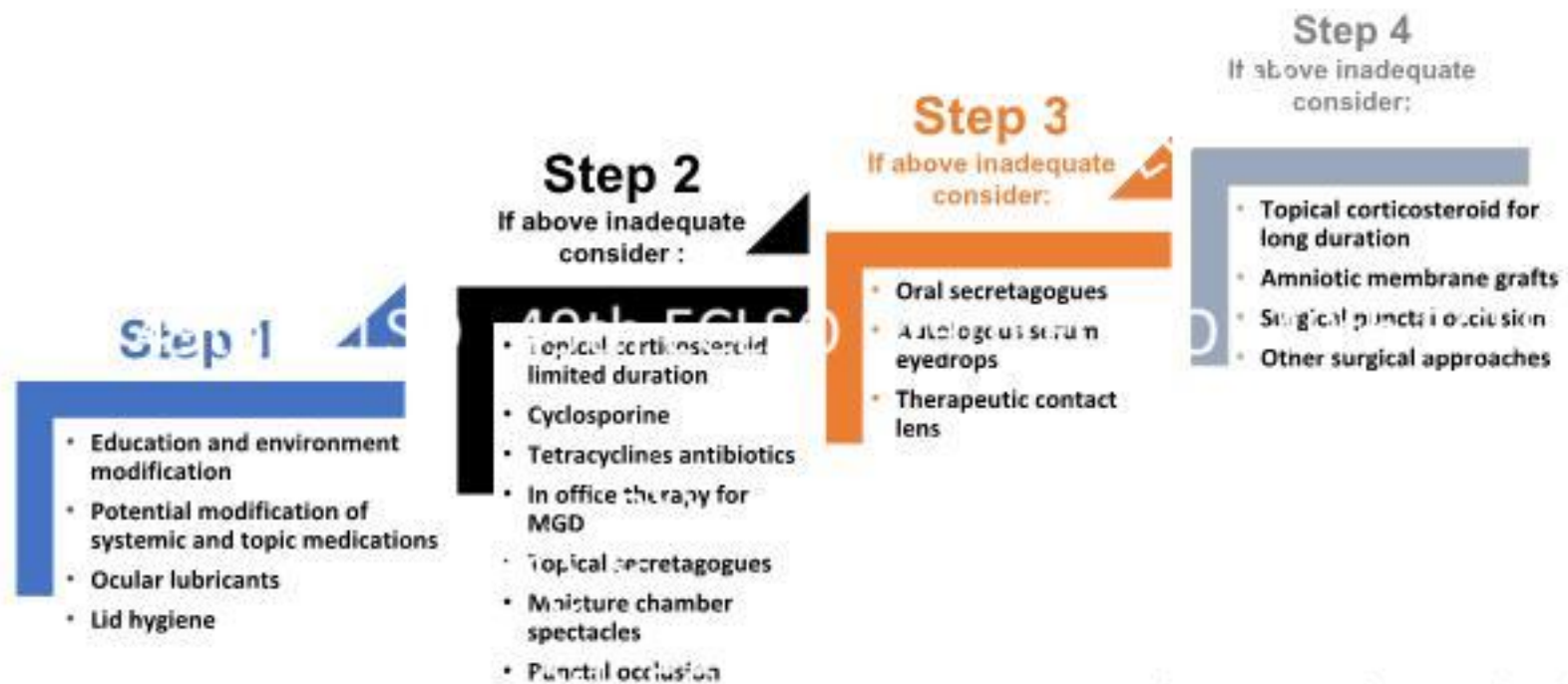
journal homepage: www.theocularsurface.com



TFOS DEWS II Management and Therapy Report

Lyndon Jones, FCOptom PhD^{a,*}, Laura E. Downie, BOptom PhD^b, Donald Korb, OD^c,
Jose M. Benitez-del-Castillo, MD PhD^d, Reza Dana, MD^e, Sophie X. Deng, MD PhD^f,
Pham N. Dong, MD^g, Gerd Geerling, MD FEBO^h, Richard Yudi Hida, MDⁱ, Yang Liu, MD^j,
Kyoung Yul Seo, MD PhD^k, Joseph Tauber, MD^l, Tais H. Wakamatsu, MD PhD^m,
Jianjiang Xu, MD PhDⁿ, James S. Wolffsohn, FCOptom PhD^o,
Jennifer P. Craig, MCOptom PhD^p

Treatment recommendations for DED



Antiinflammatory therapy should be applied as early as possible

Tear Substitutes

- Pucker AD, Ng SM, Nichols JJ. Over the counter (OTC) artificial tear drops for dry eye syndrome. Cochrane Database Syst Rev 2016;2:CD009729.
- Dissolvable Inserts (Lacrisert®)
- Combinations
 - HA + CMC
 - HA + HP-guar
 - HA + Trehalose

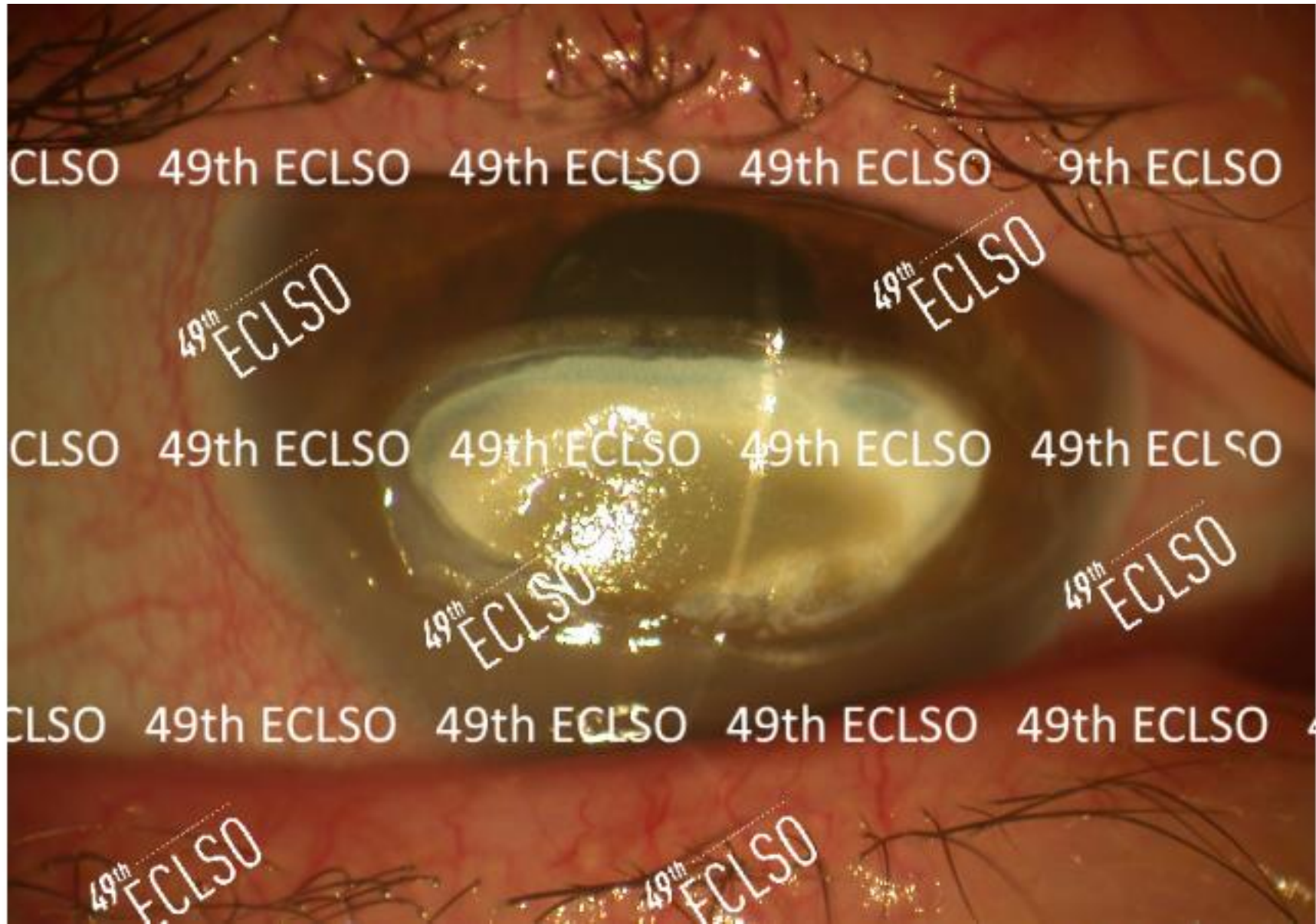


Tear Substitutes

- Osmoprotectants
 - Carnitine
 - Erythritol
 - Glycerol
 - Trehalose
- Antioxidants
 - Acetylcysteine
 - Vitamin A
 - Quercetin
 - Gallic acid
 - Selenoprotein P
- Inactive agents: buffers and electrolytes (K^+ y bicarbonate)
- Lipid supplementation
 - MGD
 - Sprays (?)



“Buffers and inactive ingredients”



CLSO 49th ECLSO 49th ECLSO 49th ECLSO 9th ECLSO

49th ECLSO

49th ECLSO

CLSO 49th ECLSO 49th ECLSO 49th ECLSO 49th ECLSO

49th ECLSO

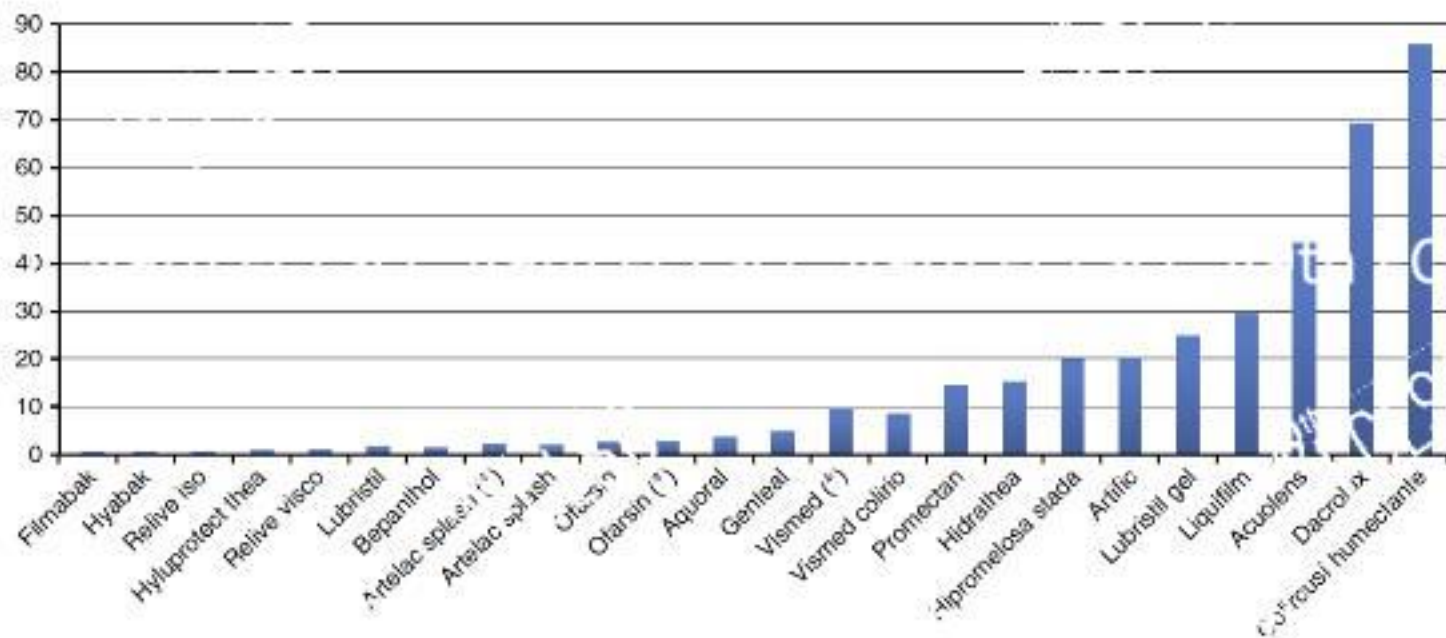
49th ECLSO

CLSO 49th ECLSO 49th ECLSO 49th ECLSO 49th ECLSO

49th ECLSO

49th ECLSO

Phosphates in spanish tears substitutes

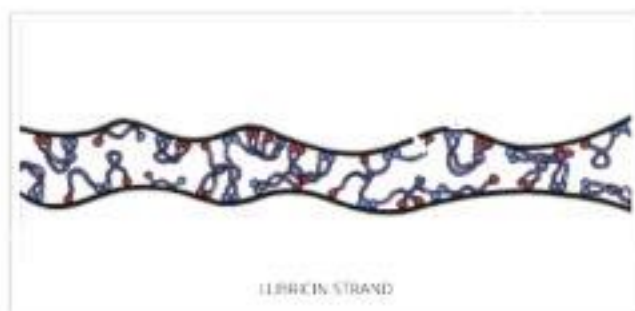


Biological Tear Substitutes

- Adults allogenic serum
- Umbilical cord serum
- Platelet preparations
- **Amniotic membrane drops**



About Lubricin



LUBRICIN : The Nonstick Molecule

Lubricin (PRG4) is a large endogenous complex glycoprotein that binds to and protects tissue surfaces from friction induced wear & damage in much the

same way that Teflon® coats and protects the surface of the non-stick pans in your kitchen – it is the most lubricating and anti-adhesive molecule in the human body.

Originally identified as a lubricating component of synovial fluid, lubricin is found on the surface of the knee cartilage, on the ocular surface and in numerous additional tissues throughout the human body – it is everywhere in the human body and is essential to proper functioning.

Inflammation caused by injury, disease and aging, impairs the body's ability to produce lubricin. Supplementation with recombinant Lubricin interrupts the destructive inflammatory cascade by eliminating friction, arresting wear-related degradation, and restoring function to these surfaces.

Lubricin is especially beneficial in the management of **dry eye** and **osteoarthritis**.

Synovial fluid

Protects surfaces from friction

Recombinant human lubricin

Lubris - Novartis

Bad news !!! 🙄

Secretagogues

- Topical:
 - Aqueous
 - Diquafosol
 - **LacriIn**
 - Mucin
 - Rebamipide
 - Galectin-3
 - MMF
 - NGF
 - Lipid
 - ILG-1
 - Topical testosterone
- Oral: Pilocarpine and cevimeline
- Nasal neurostimulation (TrueTear® and iTear100®)
- TRPM8 stimulation (AVX-012 (Avizorex) now AR-15512 (Aerie) TRPM8 agonist Phase IIb)





Diquas®



Mucosta®

News > FDA Approvals

FDA Approves First Nasal Spray for Dry Eye

Laird Harrison

DISCLOSURES | October 22, 2021



Read Comment



The first nasal spray to treat [dry eye](#) disease has won approval from the US Food and Drug Administration (FDA).

Sprayed twice daily into the nostrils, 0.03-mg [varenicline](#) solution (Tyrvaya) improves signs and symptoms of dry eye disease. It provides an alternative to the immunomodulators currently available as prescription treatments, according to Marian Macsai, MD, chief medical officer for the drug's maker, Oyster Point Pharma.

"We're super excited to bring a new treatment for dry eye disease to patients and eye care practitioners," she told *Medscape Medical News*.

The company plans to make the drug available to wholesalers in November in cartons containing two multidose nasal spray bottles. Each bottle supplies treatment for 15 days. Samples will be made available to eye care practitioners.

OC-01: a highly selective nicotinic acetylcholine receptor agonist

Lacripep[®] (Tear Solutions)



- It's a **synthetic tear protein fragment of lacritin**, which is a constituent of normal human tears, but is **lacking in the tears of DED patients**.
- Promotes tear secretion, and proliferation of epithelial cells.
- Phase I/II trial of Lacripep in primary Sjögren's syndrome patients exhibited a highly statistically significant reduction in inferior corneal staining, as well as a statistically significant improvement in burning and stinging.

Sylentis announces results of its Phase III Clinical Trial HELIX in Dry Eye Syndrome



SYL1001 = Tivanisirán

Sylentis a company to the PharmaMar group with offices and laboratories at QUBE announces results of its Phase III Clinical Trial HELIX with tivanisirán (SYL1001) for the treatment of Dry Eye Syndrome. The HELIX trial has demonstrated an improvement ($p=0.035$) in the reduction of central corneal damage.

Data will be presented to the FDA and other regulatory authorities in the second trimester of 2019 to define the regulatory strategy. Results of the HELIX trial will be presented in the next international ophthalmology meeting ARVO 2019.

Tivanisirán is an siRNA formed by two chains of Ribonucleic Acid (RNA) one of which is complementary to a segment of the messenger RNA that codes for the TRPV1 protein. Hybridisation (union) of SYL1001 with the TRPV1 mRNA results in the reduction of the translation of TRPV1. This protein has a dual function in corneal tissues as it participates in the detection, transmission and regulation of pain in the eye as well as a mediator in the innate inflammatory response; two mechanisms in the treatment and prevention of Dry Eye Syndrome.

Cornea

Safety and Efficacy Clinical Trials for SYL1001, a Novel Short Interfering RNA for the Treatment of Dry Eye Disease

José Manuel Benítez-Del-Castillo,¹ Javier Moreno-Montañés,² Ignacio Jiménez-Alfaro,³ Francisco José Muñoz-Arango,⁴ Krista Turunen,⁵ Verónica Páez,⁶ Helena Fajalá,⁷ María Victoria González,⁷ Verónica Ruiz,⁸ Beatriz Vargas,⁷ Guadalupe Pérez-Cosme,⁹ María Martínez,⁷ Ana-Carol Biesu,¹⁰ and Ana Isabel Jiménez⁷

¹Hospital Clínico San Carlos, Madrid, Spain

²Clínica Universidad de Navarra, Pamplona, Spain

³Fundación Jiménez Díaz, Madrid, Spain

⁴Hospital Universitario Ramón y Cajal, IRYCIS, Madrid, Spain

⁵The Clark Dr. Krista Turunen, Tallin, Estonia

⁶San-Julian Central Hospital, Tallin, Estonia

⁷Sylentis, Madrid, Spain

IOVS 2016

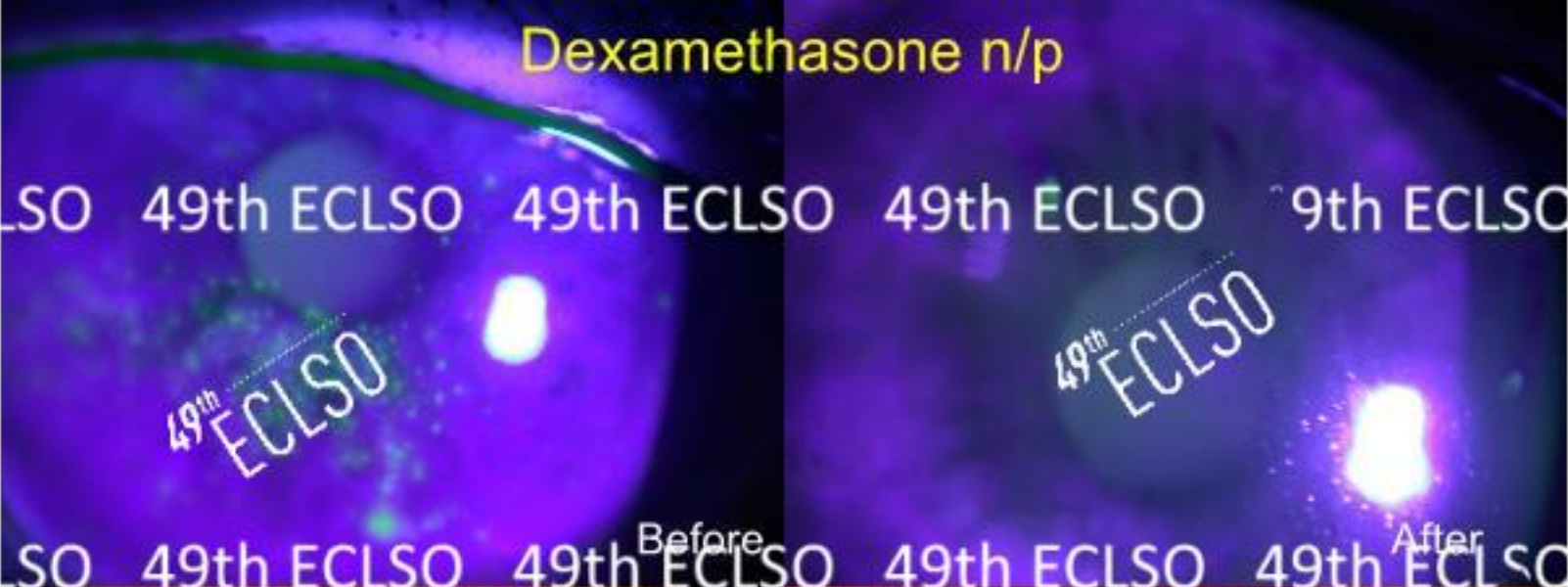
Antiinflammatory Treatment

- Steroids (soft, unpreserved)
- Ciclosporin A 0.05% (Restasis®), 0.09% (Cequa®), and 0.1% (Ikervis®)
- Tacrolimus 0.03%
- Lifitegrast 5%



Strategies to improve local CsA tolerability

- Patient education (tolerance increase with time)
- Bridging with steroids
- Use of cold tears substitutes before or after
- Cooled CsA
- If problems at bedtime change to morning





This website is intended for use by US Healthcare Professionals only.

[Important Safety Information](#) | [Prescribing Information](#) | [For Patients](#)

[Request a Rep](#)

[HOW CEQUA WORKS](#)

[EFFICACY](#)

[SAFETY](#)

[DOSING](#)

[SAVINGS & SUPPORT](#)

Change the outlook

for dry eye disease

Only CEQUA™ features NCELL™, an innovative technology that helps improve the ocular penetration of cyclosporine^{1,3}

Register for the CEQUA Professionals Network

INDICATIONS AND USAGE

CEQUA™ (cyclosporine ophthalmic solution) 0.09% is a calcineurin inhibitor immunosuppressant indicated to increase tear production in patients with keratoconjunctivitis sicca (dry eye).



Product	Company	MOA	Phase
Nivi-133	IACTA-Nanomerics	Nano-enabled form of cyclosporine A	2
ALG-1007	Allegro	Topical anti-integrin	2
EBI-005	Eleven Biotherapeutics	Topical IL-1 inhibitor protein	2
ESBA-105	Alcon Novartis	Antibody fragment against TNF alpha	2
OCS-02 (LME-636 or ESBA-1622)	Oculis-Novartis	Topical anti-TNF alpha antibody	2
ISV-101 (ISV-303, EromSite)	Sun Pharmaceutical Industries	Bromfenac low dose 0.075%	2
BOL-303242-X	Bausch + Lomb	Selective glucocorticoid receptor agonist	2

Product	Company	MOA	Phase
Cis-Urocanic	Herantis Pharma	Antiinflammatory due to inhibition of JNK	2
R-348	Rigel	JAK/SYK inhibitor	2
XG-102 and XG-104	Xigen	D-amino-acid peptide, highly selective non-competitive, long-acting inhibitor of JNK	2
Tofacitinib (CP-690,550)	Pfizer	JNK inhibitor	2
ST-266	Noveome Biotherapeutics	Proteins from cultured amnion cells modulating inflammation	2
SA-001 oral (SJP-002 topical)	Samjin Pharmaceuticals	Increase tear volume and anti-inflammatory	2

Product	Company	MOA	Phase
RX-10045	Resolvyx Pharmaceuticals	A mimetic of RvE1	2
SDP-4	SilkTech	Silk protein inhibiting inflammation	2
DA-6034	Dong-A ST Co	MMP-9 inhibitor and mucin secretagogue	2

Product	Company	MOA	Phase
CyclASol	Novaliq	New cyclosporine 0.05% and 0.1%	3
Seciera	Sun Pharmaceutical Industries	Nano-cellular formulation of cyclosporine	3
OCU-310	Ocugen	Brimonidine and steroid combination	3
EGP-437	Eyegate Pharma	Dexamethasone phosphate iontophoresis	3
KPI-121 0.25%	Kala	Mucus-penetrating particle to enhance delivery of loteprednol etabonate	3
HBM9036/HL036 Tanfanercept	Harbour/Hanall	Topical TNF alpha blocker	3
TOP-1630	TopiVert	Narrow spectrum kinase inhibitor	3

Product	Company	MOA	Phase
MIM-D3 (Tavicimide)	Mimetogen- Allergan	Partial NTRK1 agonist	3
RGN-259	RegeneRx	Tβ4 promotes cell migration, and reduces both apoptosis and inflammation	3
ADX-102 or Reproxalap	Aldeyra	Malondialdehyde inhibitor	3

Reproxalap[®] (Aldeyra)



- Is a small-molecule **reactive aldehyde species (RASP) inhibitor** that covalently binds free aldehydes and diminishes excessive RASP levels.
- Reproxalap (Phase III) has demonstrated rapid, broad and clinically relevant symptomatic control in DED patients over 12 weeks of therapy.
- There was statistically significant improvement compared to vehicle in signs of DED, as demonstrated by fluorescein staining.

RGN-259[®] (RegeneRx)



- A novel treatment for dry eye and neurotrophic keratitis.
- **Tβ4 (Thymosin-β4)** promotes cell migration, and reduces both apoptosis and inflammation.
- Phase III clinical trial (ARISE-3) didn't meet its primary outcome measures.
- However, there was a significant improvement in ocular grittiness at one and two weeks after treatment, and post-exposure in a controlled adverse environment after two weeks of treatment with the drug, compared to placebo.

CyclASol[®] (Novaliq)



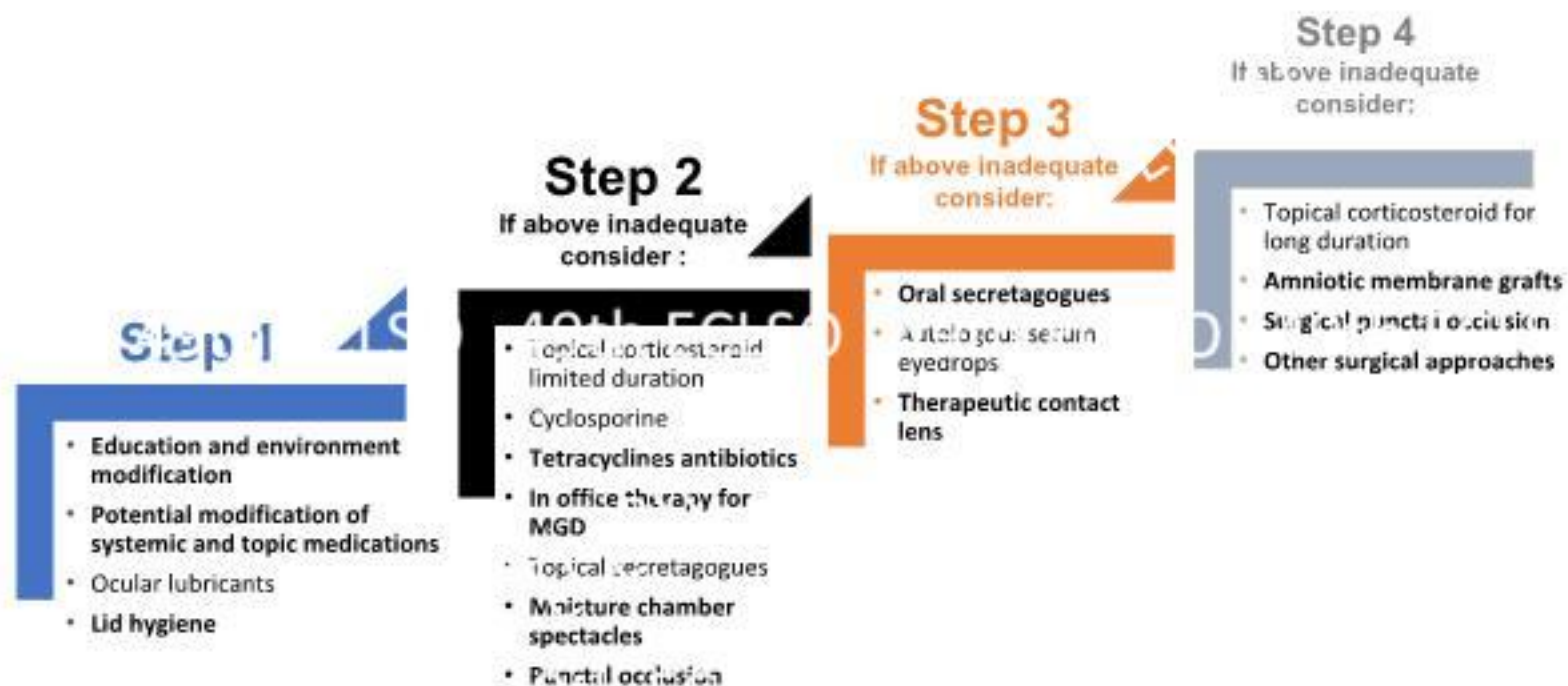
- Cyclosporine A 0.1% in EyeSol.
- Water-free drug product (**semi-fluorinated alkane vehicle**) that enhance bioavailability in comparison to water or oil-based formulations.
- Phase IIb/III trial (ESSENCE-1) demonstrated statistically significant improvements in primary endpoints for both signs and symptoms after four weeks.
- ESSENCE-2 trial is a multicenter, randomized, double-masked, vehicle-controlled clinical trial assessing efficacy, safety and tolerability of CyclASol for the treatment of signs and symptoms of DED.
- Positive results from ESSENCE-2 will allow FDA application in 2022.
- Very well-tolerated: self-discontinuation rate is well below 3 percent, and the side effects of stinging, burning and blurring are equivalent to vehicle.

Visomitin[®] (Mitotech)



- SkQ1 mechanism of action that consists of acting on the mitochondria. It belongs to the class of **cardiolipin peroxidation inhibitors** developed for the treatment of several age-related disorders.
- SkQ1 has been shown to mitigate tissue degeneration and improve tear quality deficit by targeting oxidative stress.
- VISTA-1, a Phase IIb/III clinical study in the United States (NCT03764735), found that SkQ1 showed evidence of efficacy in reducing both the signs and symptoms in dry-eye subjects.
- VISTA-2 is a multicenter, randomized, double-blind, placebo-controlled clinical study with two treatment arms, one receiving SkQ1 and one receiving vehicle administered twice daily. The study includes 610 patients in multiple centers across the United States who will receive treatment over a two-month period.

Treatment recommendations for DED: no drops



- **Education and environment modification**

- 20-20-20 rule
- Humidifiers
- Special glasses



- **Potential modification of systemic and topic medications**

- Antidepressants
- Antihistamines
- Anticholinergics
- Benzodiazepines
- 13-cis-retinoic acid
- Antiandrogens
- ...



Treatment for Lid Abnormalities

- Oral tetracyclines and macrolides
- Lid hygiene
- Demodex treatment (TTO and ivermectin)
- Warm compresses and devices: Blephasteam[®], MGDRx EyeBag[®], EyeGiene[®] mask
- MG expression: Lipiflow[®], MiboFlo[®], Jett Plasma Lift[®] ...
- IPL
- Rexion-Eye
- Intraductal probing (Maskin)
- Desbridement scaling (Blephex[®])
- Blinking abnormalities and ocular exposure treatment
- Contact lenses

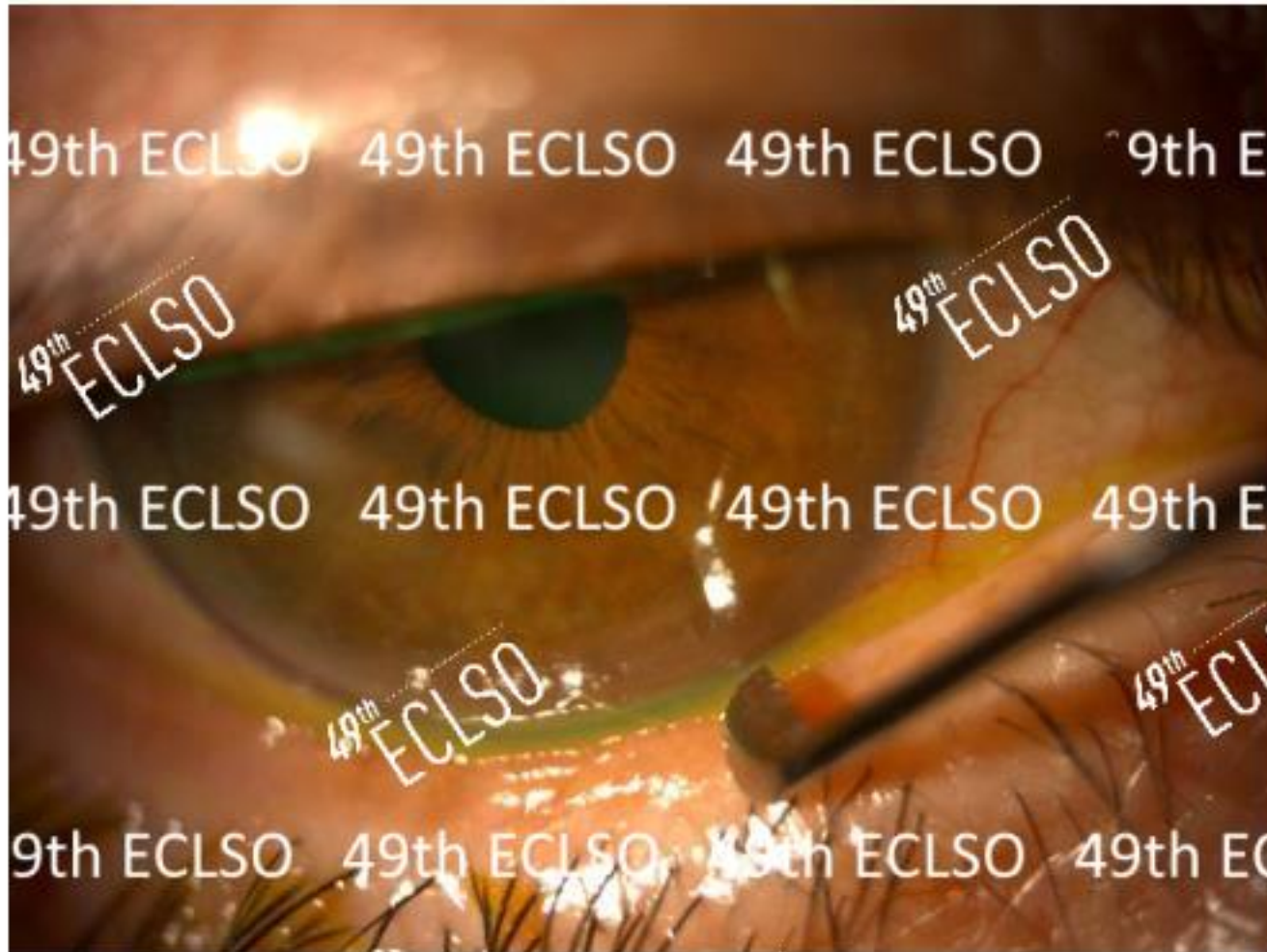


Warming ±
massage



PRODUCT	Lipiflow (J&J)	E-Eye (E-SWIN)	EyeXpress Eye Hydration System (OJBARI)	MiBoFlo Thermoflo (MIBO)	BlephEx (BLEPHEX)
					
DESCRIPTION	Sensor controlled delivery of heat and pressure to liquify and evacuate MG contents. Use a disposable contact lens that protects the eye applying heat directly to the MGs	E-Eye is a device that generates a polychromatic pulsed light for IPL treatment. The energy, spectrum and wavelength are set to stimulate the innervation and decrease inflammation of the MGs	Through the patented goggle system, the hands-free device provides uniform, constant, regulated, heat to the entire surface of the upper and lower lids. MGs are manually expressed after the session	The MiBoFlo Thermoflo employs a thermoelectric heat pump designed to liquefy inspissated secretions and improve meibomian glandular function.	The BlephEx is a handheld device that rotates a moistened medical-grade sponge at high speeds to remove excess bacteria, biofilm, and debris from the lid and unroofs the meibomian glands.
SESSIONS (PERIODICITY)	1 (every year)	3 (1, 15 and 30 days)	3-4 (every 2-4 weeks)	3 (every week)	Repeated at 4 to 6-month intervals
CE MARK	Yes Yes	No Yes	Yes Yes	Yes Yes	Yes Yes
MECHANISM OF ACTION	Therapeutic heat and compression	Intense Pulsed Light	Therapeutic heat	Therapeutic heat	Microblepharoexfoliation

PRODUCT	iLux MGD Treatment Device (ALCON)	TearCare System (SIGHT SCIENCES)	M22 (LUMENIS)	Eye-Light (TOPCON)	Thermaeye (IMEX)
DESCRIPTION	<p>The iLux is a handheld device that applies heat and compression via a sterile, single-patient use disposable Smart Tip under direct visualization to treat MGD. The Smart Tip inner pad slips behind the eyelid being treated, while the outer pad is pressed against the outer surface of the eyelid. 8 minutes</p>	<p>The TearCare System consists of an electrothermal controller that delivers regulated and adjustable heat via single-use iLid devices that are affixed to the upper and lower lids. The iLid devices contain multiple thermal sensors that adjust to the lid and allows for natural blinking. It is packaged with a disposable eyelid expression forceps for manual MG expression</p>	<p>A modular platform with over 30 dermatologic and aesthetic indications, Intense pulsed light has shown improvement in MGD and dry eye disease</p>	<p>Eye-Light (IPL) has been identified to treat MGD, which has been used for several years in dermatology. IPL applied on the periorbital and cheekbone areas, triggers the stimulation of neurotransmitters, these solicit the MGs to produce meibum, reducing the evaporation. Eye-Light includes a Low Level Light Therapy) dry eye treatment mask. No gel</p>	<p>Thermaeye reduce MG inflammation and Demodex infestation. It employs LIUR (Ultra Controlled Intense Light), a micropulse system that allows natural cooling of the skin, this permits treating any type of skin colour without using different filters</p>
SESSIONS (PERIODICITY)	1		4 (very 2 weeks)	3 (1, 15 and 30 days)	3 (1,15 and 30 days)
FDA	Yes	No	Yes		No
CE MARK	No	No	Yes	Yes	Yes
MECHANISM OF ACTION	Therapeutic heat and compression	Therapeutic heat	Intense Pulsed Light	Intense Pulsed Light	Intense Pulsed Light

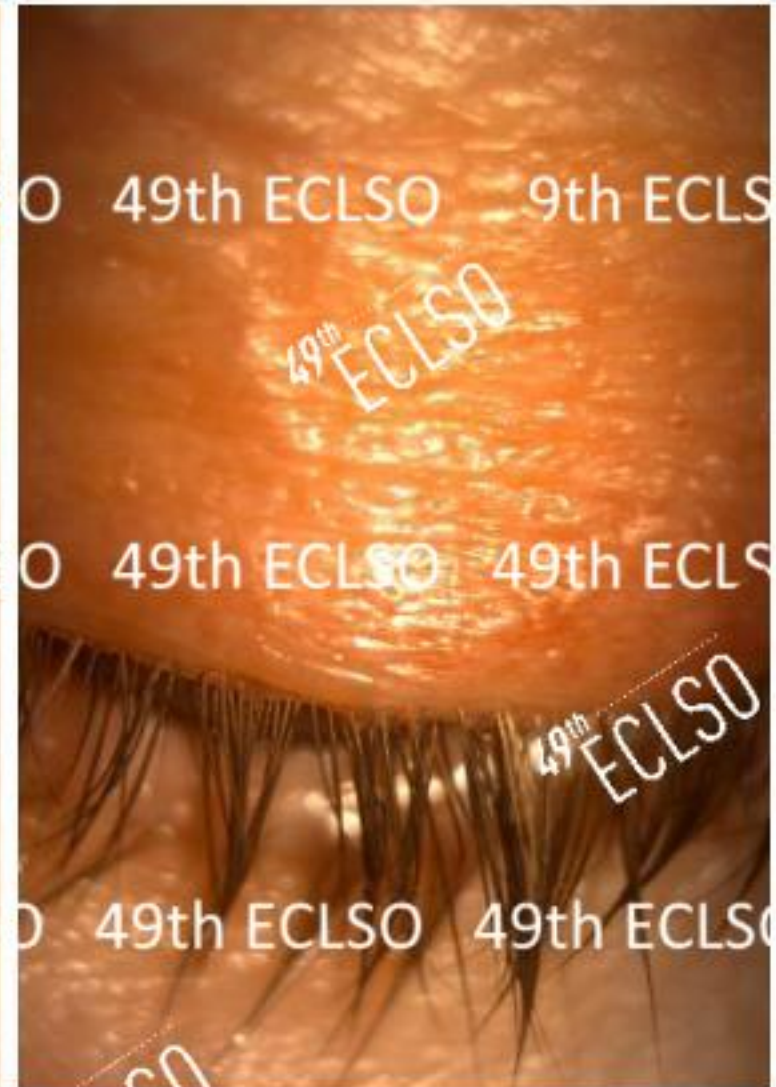


Debridement scaling



BlephEx

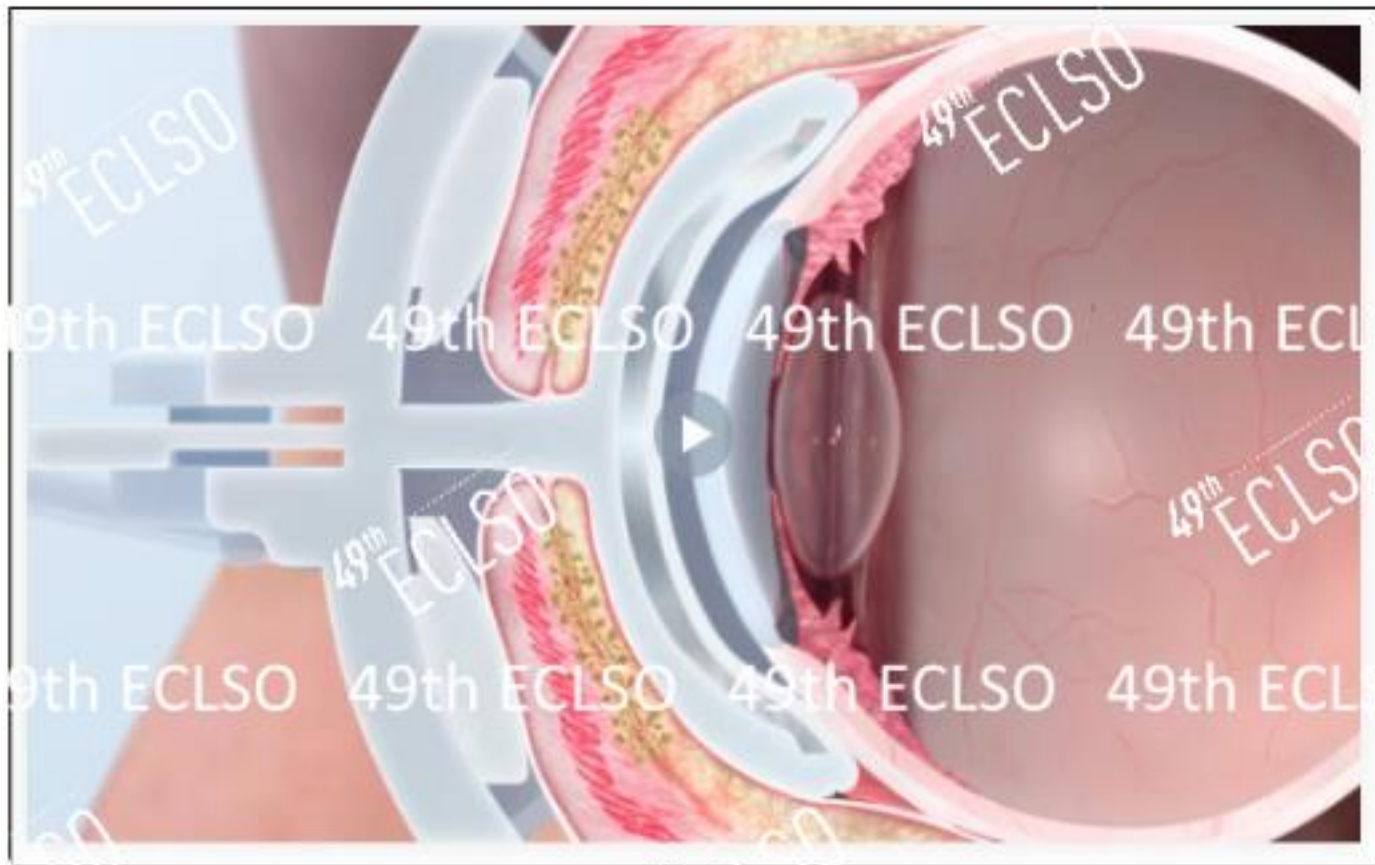
Before



After



LIPIFLOW® THERMAL PULSATION SYSTEM



Report Date: 1/25/2018 11:28:42 PM
LipiView® Serial Number: 02298

Lipid Imaging Report

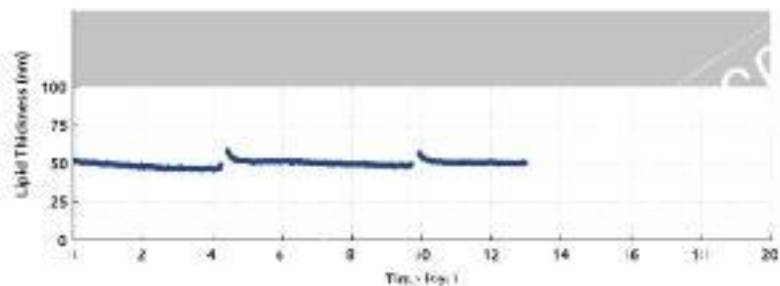
CLINICAL EVENT: RP
MADRID
913063030

Patient: [REDACTED] SO 4 AUGUSTO (2/21/1946)

Face ID: [REDACTED] SO 4
1/9/2018 7:44:24 PM - LipiView® Serial Number: 02298



Average LLT:	60 nm	Inter-LBLI: %	0 / 2
Maximum LLT:	77 nm @ frame 121	CFI: %	7.24
Minimum LLT:	46 nm @ frame 121	Standard Dev:	2



Report Date: 1/25/2018 5:41:30 PM
LipView® Serial Number: 02298

Lipid Imaging Report

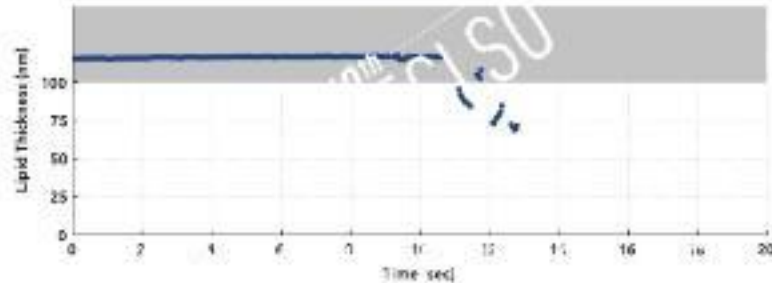
CLINICAL EVENT: RP
ALMAGDO 30
MADRID
913063030

Patient: [REDACTED] CLSO AUGUSTO (2/21/1946)

Face ID: [REDACTED] CLSO
1/9/2018 6:34:33 PM - LipiView® Serial Number: 02298

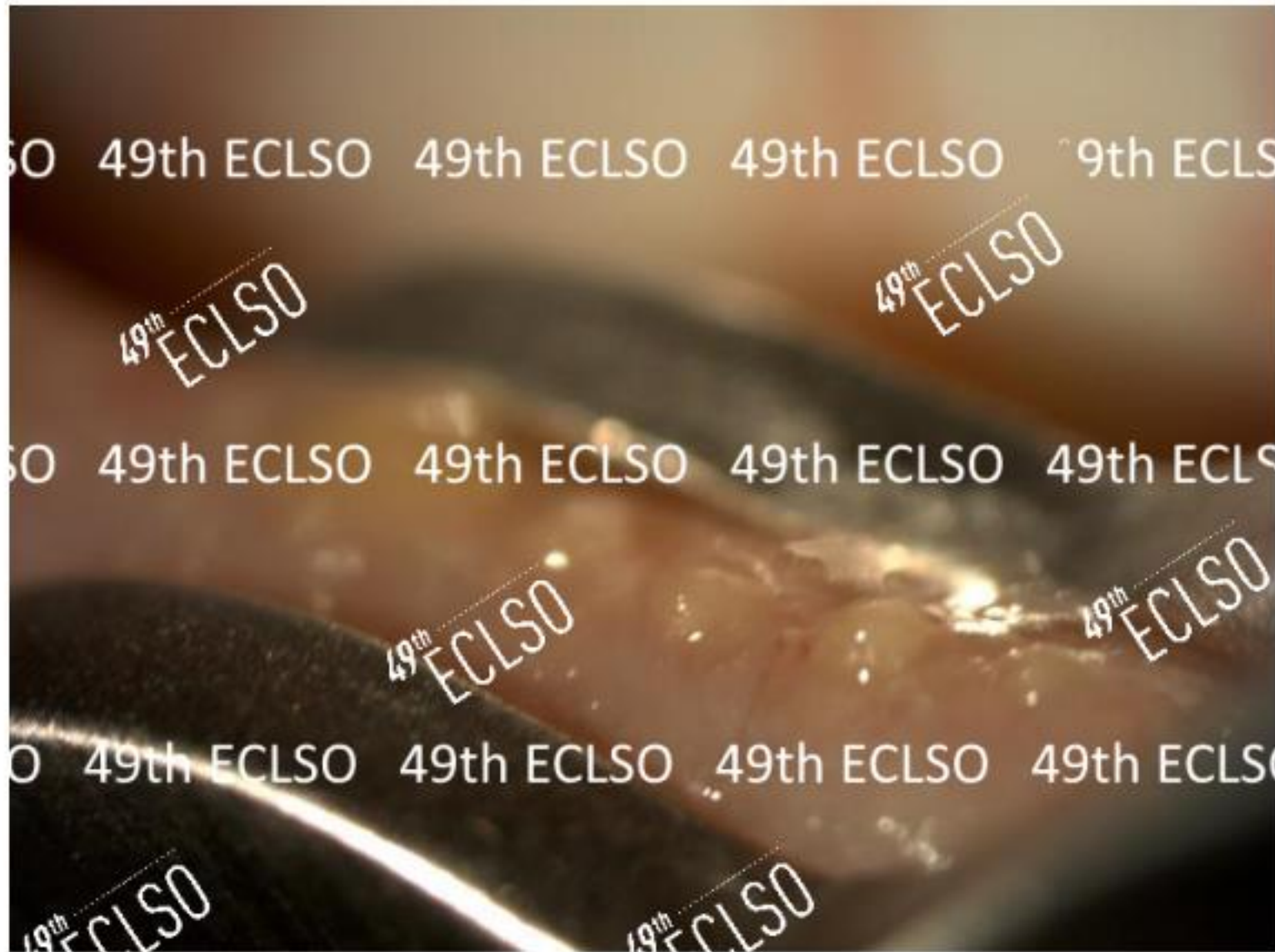


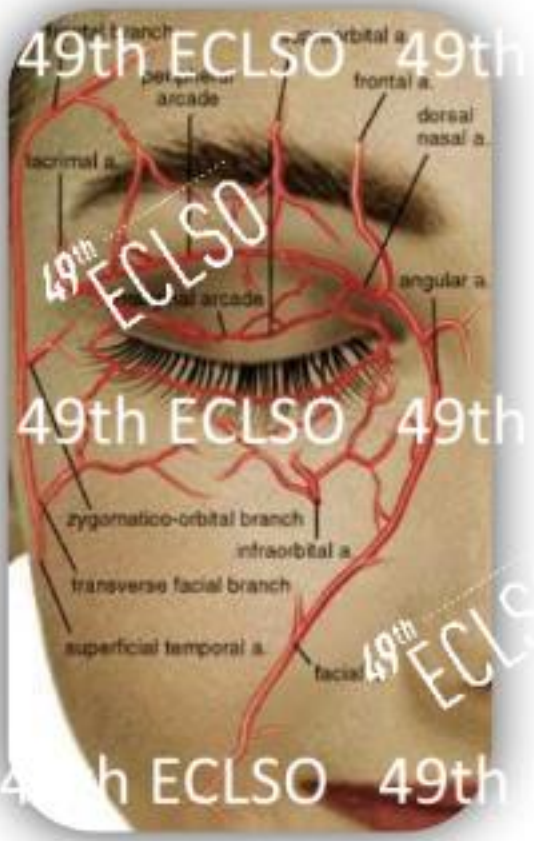
Average LLT:	106 nm	Perturb: %	1 / 2
Maximum LLT:	107 nm @ frame 20	CFI: %	0.54
Minimum LLT:	63 nm @ frame 302	Standard Dev:	10





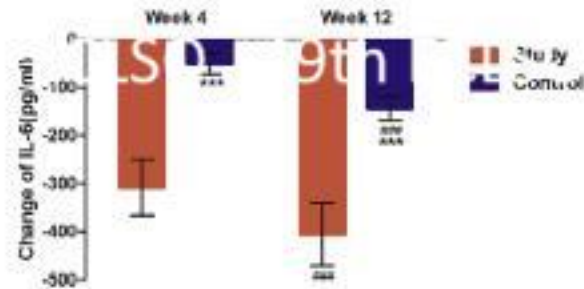
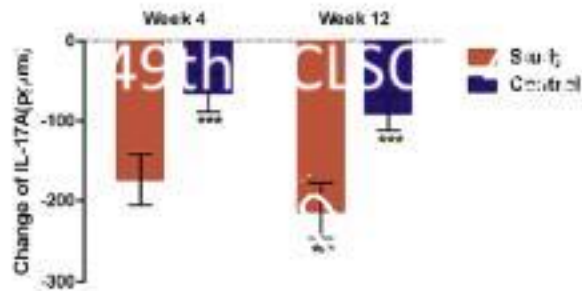
Intense
Pulsed
Light



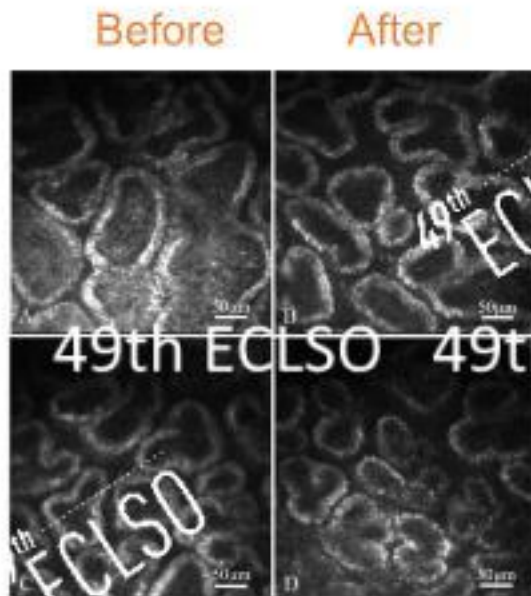


IPL MoA

- Hypoxia
- Antiinflammatory:
 - Telangiectasia are source of inflammatory cytokines
 - Decrease iL6, iL17A, and PGE2 (Liu et al AJO 2017)
- Warming
- Parasympathetic stimulation
- Antiparasitary (Demodex) and Antimicrobial (Bacillus Olerinus)
- Analgesic and biostimulator



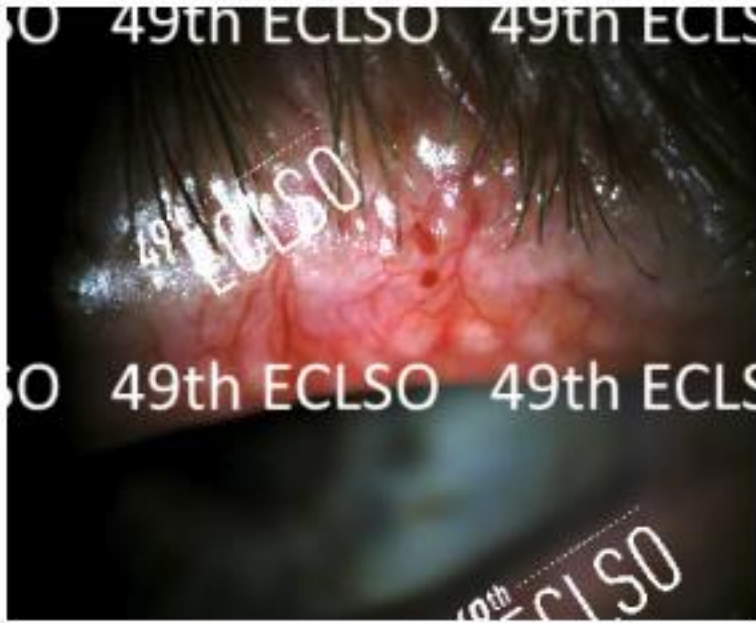
Liu R, et al AJO 2017



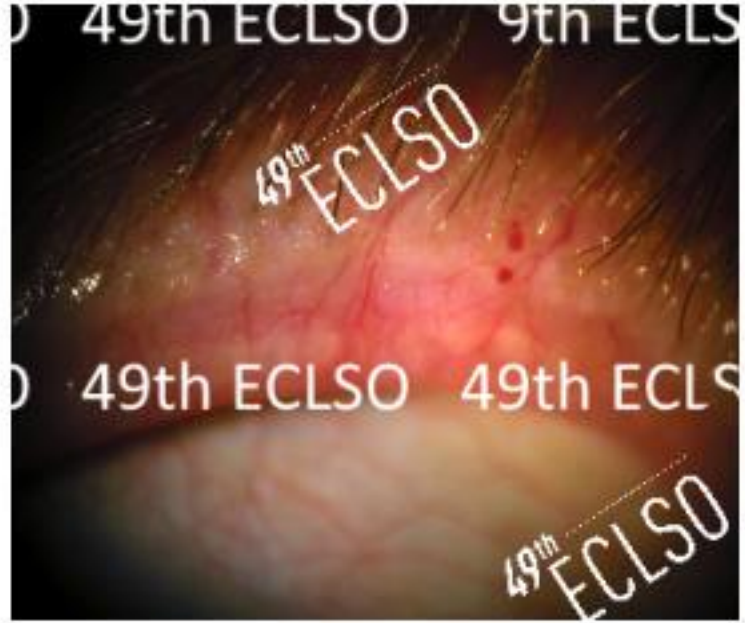
Yin Y, et al Curr Eye Res 2018

Maskin's Probing





Before



After

Jett Plasma Lift®

- Warming
- Remove hyperkeratinisation



Rexon-Eye®

CLINICAL SCIENCE

Cornea 2019

High Frequency Electrotherapy for the Treatment of Meibomian Gland Dysfunction

Giulio Ferrari, MD, PhD, Annalisa Colucci, MD,* Marco Barbariga, PhD,*
Alfredo Buggeri, PhD,†† and Paolo Rama, MD**

- Quantum molecular resonance (QMR)
- Biostimulation



Dietary Modifications

- General hydration state
- Lactoferrin
- Calorie restriction
- Diet
- Omega 3, 6 and 3+6 (resolvins)
 - Anti-inflammatory
 - Neuroprotector (neuropathic pain)
 - Ng SM, Lindsley K, Akpek EK. Omega-3 and omega-6 polyunsaturated fatty acids for dry eye syndrome (Protocol). Cochrane Database Syst Rev 2014;3: CD011016



THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

n-3 Fatty Acid Supplementation
for the Treatment of Dry Eye Disease

The Dry Eye Assessment and Management Study Research Group*

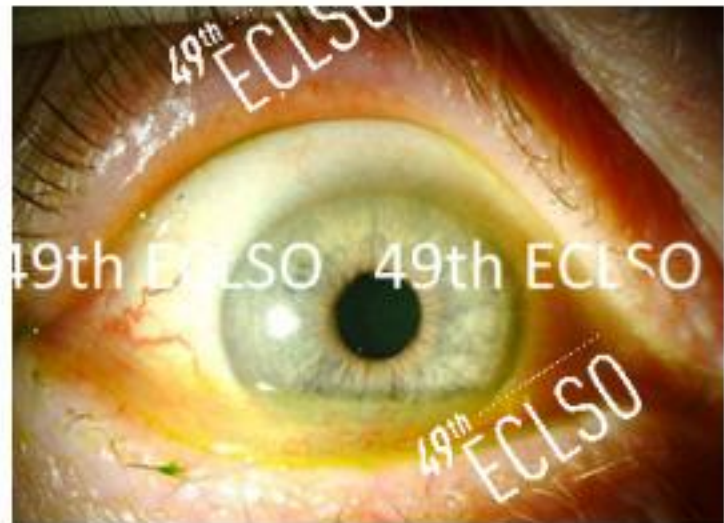
Others

- Milk
- Honey : Manuka
- Acupuncture
- Management of psychological aspects
- Happiness and physical activity



Surgery

- Tarsorrhaphy
- Surgery for conjunctivochalasis
- Botulinum toxin
- Dermatochalasis
- Amniotic membrane grafts
- Dacryoreservoirs
- Salivary gland transplantation



**Good news
for our DED
patients**



Thanks

th ECLSO 49th ECLSO 49th ECLSO 49th ECLSO 9th ECLSO 49

49th
ECLSO

49th
ECLSO

th ECLSO 49th ECLSO 49th ECLSO 49th ECLSO 49th ECLSO 49

49th
ECLSO

49th
ECLSO

th ECLSO 49th ECLSO 49th ECLSO 49th ECLSO 49th ECLSO 49

49th
ECLSO

49th
ECLSO