SEPTEMBER 16, 2016
Vol. 3, No. 13

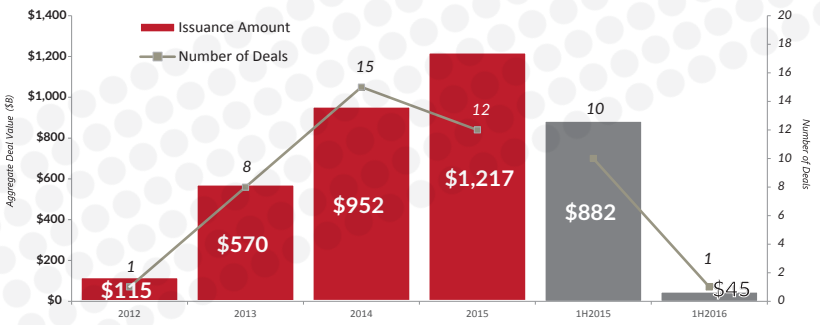
The MedTech STRATEGIST

Published by Innovation In Medtech, LLC

MARKET TRACK

See page 36

Medical Device & Diagnostics IPOs, 2012-1H 2016



Device Innovations Target Fast-Growing DRY EYE MARKET

Device-based treatments are beginning to gain headway in the large and expanding dry-eye market, a space that has historically been dominated by prescription drugs and over-the-counter remedies.

by
MICHAEL LACHMAN

An estimated 30 million Americans are afflicted with dry eye to some degree and the number of treatment options for this condition is beginning to expand as companies look for ways to tap into this large and underserved market. They have good reason to pursue this opportunity: in the 13 years since FDA approval of *Restasis* (**Allergan plc**), the first prescription eye drop for dye eye, *Restasis* sales have grown steadily, reaching $1.3 billion in 2015 (*see Figure 1*). *Restasis* lost its US market exclusivity when **Shire plc**'s new dry eye drug, *Xiidra*, won a hard-fought FDA approval in July. However, both of these drugs could one day find themselves competing with device-based treatment options, which are also gaining traction in this space. Two devices in particular—the *LipiFlow System* from **TearScience** and the *Oculeve Intranasal Tear Neurostimulator* from Allergan (the latter belongs to a small but growing group of ophthalmic neurostimulation technologies)—are attracting considerable attention and could play a significant role in future treatment paradigms.

A Multifactorial Disease

Dry eye is a multifactorial disease that leads to ocular discomfort and reduced visual acuity, and in severe cases can damage the ocular surface. Of the estimated 30 million Americans suffering from dry eye, about 60% have mild or episodic disease, 30% have moderate disease, and about 10% have severe dry eye. Dry eye prevalence is positively correlated with older age and with

female gender and can also be associated with contact lens wear, certain medications, and environmental factors.

There are two basic categories of dry eye. Aqueous tear-deficient dry eye is characterized by an inadequate amount of tear production by the lacrimal glands. Evaporative dry eye is characterized by poor quality of tears, particularly due to an insufficient amount of oil or lipid that typically slows the rate of tear evaporation and keeps tears stable. An important but often overlooked and under-treated cause of evaporative dry eye is meibomian gland dysfunction (MGD), in which the tiny oil glands that line the edges of the eyelids become obstructed or secrete oil of poor quality. Although evaporative dry eye is more prevalent than aqueous tear deficiency, these two dry eye subtypes are not mutually exclusive; they coexist in a large percentage of dry eye patients.

High Regulatory Hurdles

Both *Restasis* and *Xiidra* address aqueous deficiency by blocking the inflammatory cascade that can lead to reduced tear production. There are a number of other drugs in various stages of development for dry eye (*see Figure 2*); however, *Xiidra*'s bumpy road to the US market sets a cautionary tone.

In recent years, the dry eye market has been characterized by high regulatory hurdles and pipeline setbacks. *Xiidra* itself was the subject of complete response letter (CRL) from the FDA in 2015 requesting an additional clinical trial from Shire.

There are several challenges in designing clinical trials for dry eye therapies, including the fact that dry eye itself is a heterogeneous, multifactorial condition that is not fully understood. While the FDA requires efficacy to be demonstrated for both dry eye signs (as measured by diagnostic tests) and symptoms (as reported by patients), in many populations, signs and symptoms do not correlate, so it can be difficult to show improvement in both in a single study. There are also placebo and vehicle effects that lead to better-than-expected outcomes in study control groups. Additional confounding factors include subjectivity and variability in measurement of dry eye signs and symptoms.

Shire pursued a unique and expensive regulatory approach with *Xiidra* by addressing signs and symptoms in separate studies instead of a single study. Given the FDA requirement for confirmatory studies, this resulted in four clinical trials instead of two, involving over 2,000 patients. The result of this process was a strong label for *Xiidra*, which is the first prescription drop approved to treat both the signs and symptoms of dry eye.

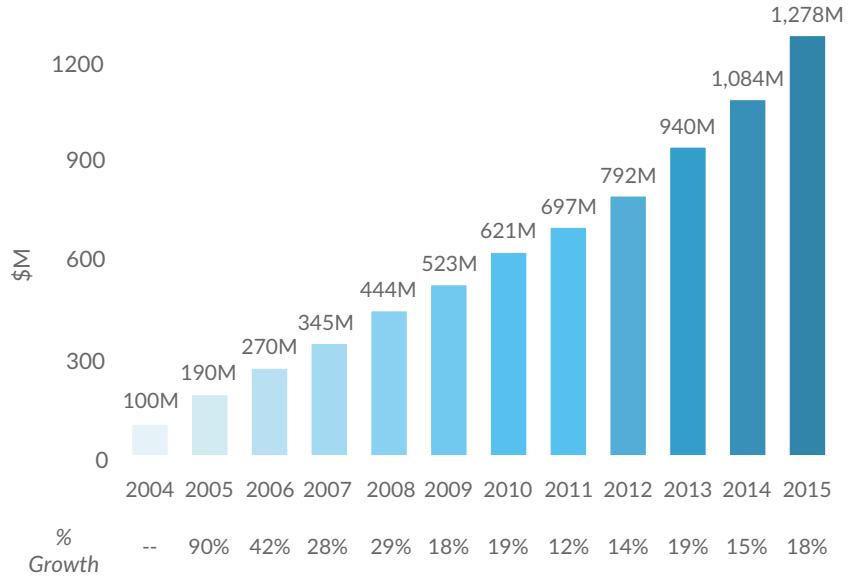
Device-Based Treatments on the Rise

Although dry eye treatment is typically viewed as a market dominated by prescription eye drops and over-the-counter lubricants, device-related treatments also have come to the forefront in recent years. The two highest profile devices addressing this market target each of the two primary dry eye clinical mechanisms. The *LipiFlow System* from TearScience, which received 510(k) marketing clearance from the FDA in 2011 and is the most commercially advanced device-based treatment, directly addresses MGD and evaporative dry eye, while the *Oculeve Intranasal Tear Neurostimulator* from Allergan, which is awaiting FDA approval, directly addresses aqueous deficient dry eye and tear production.

In addition, in the area of drug delivery, **Ocular Therapeutix** is in Phase 2 development with *DEXTENZA*, a steroid-eluting hydrogel depot for inflammatory dry eye. The device is inserted noninvasively into the canaliculus of the eyelid and delivers a four week, tapered-release dose of dexamethasone to the ocular surface as the hydrogel resorbs. *DEXTENZA* is also in Phase 3 development for the

Figure 1

Restasis Worldwide Revenues (2004-2015)



Source: Allergan

treatment of postoperative inflammation and pain and for allergic conjunctivitis.

TearScience's LipiFlow

First-line treatments for MGD typically involve eyelid hygiene: use of warm compresses (sometimes with light pressure or massage) and eyelid scrubs with mild soap. Dietary supplementation with omega-3 fatty acids may also improve oil production by the meibomian glands. However, these traditional treatments are often not sufficient to fully resolve MGD. *LipiFlow* from TearScience is the only FDA-cleared device for MGD that has been shown to restore gland function. The *LipiFlow Activator* is a single-use device that is connected to a console and inserted under the upper and lower eyelids by an eye care professional. During a 12-minute procedure, the device applies heat and pulsed pressure to the inner eyelid to remove gland obstructions while insulating the corneal surface from heat and pressure transmission.

A study published this year involving 400 eyes (200 subjects) showed that a single *LipiFlow* treatment delivered sustained three-fold improvement in meibomian gland function and 50% reduction in dry eye symptoms over the full study duration of 12 months. Physicians often tell patients that they may benefit from re-treatment within one to three years.

Patients typically pay about $400-$500 per eye for *LipiFlow* treatment, which is currently not covered by most insurers. In order to make the technology more accessible to both physicians and patients and to drive greater usage, TearScience cut its prices for equipment and disposables by 50% in 2015. This change in pricing strategy appears to be generating accelerated growth: approximately 90,000 *LipiFlow* treatments had been performed by the end of 2015 and the company expects an even greater number of treatments to be performed in 2016 alone.

The *LipiFlow System* is supported by a suite of diagnostic tools to help eye care professionals evaluate MGD. *LipiView II with Dynamic Meibomian Imaging (DMI)* provides high-definition images of gland structure, measures lipid layer thickness, and evaluates blink dynamics. *LipiScan with DMI* is a new dedicated, rapid HD gland imager designed to improve workflow.

Figure 2

Selected Dry Eye Pharmaceutical Pipeline Products

Company	Product/Molecule	Mechanism of Action	Stage/Status
Eleven Biotherapeutics	Isunakinra (EBI-005)	IL-1 receptor inhibitor	Phase 3
Eyegate Pharma. (Jade Therapeutics)	Cross-linked hyaluronic acid - CMHA-S (JDE-003)	Long duration lubricant	Pre-clinical
Herantis Pharma	Cis-urocanic acid (cis-UCA)	Anti-inflammatory and cytoprotective	Phase 2
Kala Pharmaceuticals	Loteprednol etabonate nanoparticle (KPI-121)	Mucus-penetrating particle (MPP)	Phase 2
Mimetogen Pharma.	Tavilermide (MIM-D3)	TrkA agonist	Phase 3
Mitotech SA	Visomitin (SkQ1 eye drops)	Mitochondria addressed antioxidant	Phase 3
Novaliq GmbH	CyclASol - Cyclosporine A in semi-fluorinated alkanes (SFA)	Immunosuppressive and anti-inflammatory	Phase 2
Ocular Therapeutix	Sustained release dexamethasone (DEXTENZA)	Anti-inflammatory; intracanalicular depot	Phase 2
Otsuka Pharmaceutical	Rebamipide (OPC-12759E)	Mucin secretogogue	Phase 3 (JP)
ReGenTree LLC	RGN-259	Thymosin beta 4 (Tβ4)	Phase 3
Santen	Cyclosporine A cationic emulsion (Cyclokat)	Immunosuppressive	Phase 2/3
Seikagaku Corp.	Modified hyaluronate (SI-614)	Long duration lubricant	Phase 2/3
Sucampo Pharma. (R-Tech Ueno)	Recombinant human serum albumin (RU-101)	Mucin production	Phase 2

Source: Company reports

Allergan's Oculeve Stimulation Device

The *Oculeve Intranasal Tear Neurostimulator* is a novel device for dry eye treatment that was developed by Oculeve, Inc., a privately held company that began as a multidisciplinary collaboration between the Stanford University Biodesign Center and Stanford's Department of Ophthalmology. Last year, Allergan acquired Oculeve for $125 million cash plus commercialization-based milestone payments. In May of this year, Allergan announced that the device met its primary and secondary efficacy endpoints and showed a positive safety profile in two pivotal trials involving more than 200 adult patients. In July, Allergan filed a *de novo* application for FDA approval of *Oculeve*. Final US marketing approval is possible in 2017, although the timeline is uncertain given that there are fewer regulatory precedents and less FDA guidance for dry eye devices than for drugs.

Under normal circumstances, sensory stimulation of the ocular surface leads to an autonomic reflex that results in tear secretion. In patients with dry eye disease, this neural signaling of tear secretion may be disrupted due to factors such as decreased corneal sensitivity, nerve damage, or certain topical medications. The *Oculeve* device consists of a reusable, rechargeable handheld base unit, with a daily-use disposable tip, that is inserted by the patient into the nostrils. There are five levels of patient-adjusted stimulation that generate a tingling sensation. The device stimulates the trigeminal nerve inside the nasal cavity, which is responsible for about one-third of resting tear production. This activates the nasolacrimal reflex, resulting in a temporary increase in tear secretion.

During a panel discussion at the Ophthalmology Innovation Summit in May, Michael Ackermann, PhD, VP of Neurostimulation at Allergan and previously the founder and CEO of Oculeve, noted that a single use of the device seems to provide about four hours of symptomatic relief. "Anybody who has put too much wasabi on their sushi knows exactly what this is," Ackermann said. "In movement disorders and pain management, neurostimulation is a multibillion dollar industry and it's been around for a long time, but it's new to ophthalmology," he continued. "What we're finding from the practitioner and patient perspective is, at the end of the day, if it works, it works—patients feel better, they see the response."

Michael Lachman is president of EyeQ Research, which provides strategic advisory and market research/analytics to the ophthalmic industry. He is a Contributing Writer for *The MedTech Strategist.* (Email: Michael@EyeQResearch.com)