In Dry Eye, A Variety Of Mechanisms Pursue Established Therapies

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Executive Summary
Market Snapshot: Kala's Phase III nanoparticle along with Aldeyra's aldehyde trap drug and Ocugen's brimonidine/steroid combo, both in Phase II, are among the candidates pursuing Restasis and Xiidra.

While **Allergan PLC** and **Shire PLC** are jockeying for supremacy in the dry eye disease space, with the former's *Restasis* (cyclosporine ophthalmic emulsion) losing market share to the latter's *Xiidra* (lifitegrast), a host of other companies have candidates in clinical development for dry eye addressing a wide variety of targets in the hopes of bettering the existing therapies or benefiting an underserved niche.

Allergan, Shire Battle In Dry Eye As Generics Advance
By Joseph Haas 15 Jan 2018

Market Snapshot: Shire is pushing Xiidra hard to take market share away from Allergan's well established Restasis, but the pending arrival of a generic Restasis throws a curveball into the whole category.

Read the full article here

Shire, which in 2016 launched Xiidra, the first drug approved to treat the signs and symptoms of dry eye, has been trying to expand the market with disease-awareness efforts. Restasis, approved in 2002, has flourished into a blockbuster with an indication to increase a patient's natural ability to produce tears. The market's growth trajectory has been encouraging, but now there is a twist in the plan: Restasis is expected to face generic competition in the US in 2018, which will present implications for the whole category.

According to Biomedtracker, of the 27 drug candidates in clinical development for dry eye, eight are currently in Phase III, including **Kala Pharmaceuticals Inc.**'s KP-121 0.25%, a nanoparticle loteprednol etabonate formulation that employs its proprietary mucus-penetrating particle (MPP) technology. Another 18 have advanced into Phase II, including **Aldeyra Therapeutics Inc.**'s aldehyde trap drug reproxalap (ADX-102) and privately held **Ocugen Inc.**'s brimonidine/steroid combination OCU310.

Datamonitor Healthcare analyst David Dahan told *Scrip* that he expects 2018 to be a catalyst-filled year in dry eye, with a number of companies possibly reporting Phase III data, including **Sun Pharmaceutical Industries Ltd.** with *Seciera*, a nanocellular formulation of cyclosporine, the active ingredient in Restasis. Meanwhile, Allergan's post-Restasis strategy in dry eye comprises a pair of Phase III candidates: the partial neurotrophic tyrosine kinase inhibitor 1 (NTRK1) agonist tavilermide (MIM D3), partnered with **Mimetogen Pharmaceuticals Inc.**, and AGN-195263, a novel topical candidate with an undisclosed target and mechanism of action.

Recent Deal-Making In Dry Eye Disease
According to Strategic Transactions, there have been five license or option deals for dry eye disease candidates since 2013, including a **Valeant Pharmaceuticals International Inc.**/Mimetogen deal whose rights transferred over to Allergan.

- Shire paid $20m up front in May 2017 for global development and commercial rights to **Parion Sciences Inc.**'s Phase II P321, an epithelial sodium channel (ENaC) inhibitor. [See Deal]
- Despite that deal granting exclusive global rights to Shire, Parion negotiated an exclusive option for PD321 in certain Asian markets to **Santen Pharmaceutical Co. Ltd.** in July 2014. [See Deal] Santen has not taken up that option to date.
- Valeant affiliate **Bausch & Lomb Inc.** paid an undisclosed upfront fee to Mimetogen in 2013 for an option on exclusive worldwide rights to MIM D3. [See Deal]

- As part of an existing collaboration with **Novartis AG**, **BioLineRx Ltd.** licensed exclusive rights to the preclinical candidate BL 1230, a cannabinoid receptor type 2 agonist, from **Yissum Research Development Co. Ltd.** in 2016. [See Deal] Novartis has right of first refusal to three BioLineRx candidates, potentially including BL 1230, under a 2014 collaboration. [See Deal]
- Start-up **IACTA Pharmaceuticals Inc.** obtained North American rights to preclinical NM133, a nano-enabled form of cyclosporine A, from **Nanomerics Ltd.** in January 2017. [See Deal]

Mumbai, India-based Sun announced Dec. 27 that the US FDA had accepted its new drug application (NDA) for review, setting the review deadline for this August. The company claims Seciera will offer improved tear production and faster onset of action, which Dahan said was an issue with Restasis that had given Xiidra a significant advantage. With so many candidates and MOAs in progress, he thinks combination therapy is a likely outcome longer-term in dry eye disease. "Dry eye is thought to be heterogeneous so maybe different products will work better for different cases," he said. "Definitely Restasis is too slow, it takes too long and people give up on it before it kicks in."

The availability of a generic version of Restasis could make the market dynamics more challenging, however.

Kala Seeking Better Dry Eye Symptom Data

Kala is developing KPI-121 0.25% to treat the signs and symptoms of dry eye – in 2015, the Boston-area firm reported that the eye drop met the primary endpoint of bulbar conjunctival hyperemia, a sign of dry eye, and showed "promising trends" for the symptom endpoint of ocular discomfort in a Phase II study. (Also see "Kala's lead product shows promise in two eye indications" - Scrip, 2 Apr, 2015.) In addition, the biotech is developing KPI-121 1% to treat post-ocular surgery pain and inflammation.

It filed an NDA with FDA for that indication on Oct. 25 and expects to bring that product to market first.

Kala CEO Mark Iwicki told Scrip that KPI-121 is being developed for the temporary relief of the signs and symptoms of dry eye, which could be an important point of differentiation for the nanoparticle, since Restasis and Xiidra both are intended for maintenance treatment of the disease. He hopes the eye drop will be the first approved therapy for so-called dry eye flares.

Kala CEO Mark Iwicki

Source: Kala Pharmaceuticals Inc.

"There is no treatment approved by FDA to treat what is thought to be the biggest group of dry eye sufferers, and that is the episodic group of dry eye sufferers," Iwicki said. "The thought leaders will tell you that the majority of people do not have continual dry eye symptoms that require maintenance therapy, and that most people suffer from [a few] episodes of dry eye during the year. If you're mild, that might be one or two episodes a year, if you're moderate, maybe five-to-nine episodes a year, and then more severe may have more episodes."

A potent ophthalmic steroid, KPI-121 offers an ideal profile for treating flares, the exec added, because of its rapid onset of action. While both Restasis and Xiidra take weeks or months to work, KPI-121 shows an effect in the first few days of dosing, he said, and the Phase III trials are using an endpoint to measure efficacy at the end of two weeks of treatment.

"Our product is rapid-acting; it's a very comfortable drop; it has a broad anti-inflammatory spectrum of activity whereas other anti-inflammatories may hit only one or two anti-inflammatory pathways and therefore they take a while longer to work," Iwicki said. Loteprednol is the active ingredient in Valeant's *Lotemax* – offered as both an eye drop and a gel for redness, itching and watering of the eyes due to allergies, infection or the aftermath of ocular surgery.

Kala sees its candidate as a potential first-line therapy in dry eye, a progressive disease in which many patients start with a few flares a year, but often the frequency increases, he added, sometimes leading to the need for maintenance therapy. Kala reported Jan. 5 that KPI-121 0.25% hit both the sign and symptom endpoint in the Phase III STRIDE 1 study, and in STRIDE2 it hit the sign endpoint but missed statistical significance for the symptom of ocular discomfort severity at day 15 – although the firm said it showed some improvement.

KPI-121 also missed the symptom endpoint in Phase II. Before the Phase III data were unveiled, Iwicki conceded that FDA guidance requires a dry eye drug to hit statistical significance for both a sign and a symptom of dry eye but added that the Phase II study was not sufficiently powered to show statistical significance for ocular discomfort, he said.

"We did hit hyperemia with a very strong p-value, and saw a very encouraging trend on ocular discomfort," the exec noted. "As we looked at the full dataset, we saw that endpoints in general were moving in the same direction."

Kala had hoped to file an NDA for dry eye during the first half of 2018, but following the STRIDE2 disappointment the company allowed that it may need to do another Phase III trial. Kala plans to review the totality of its Phase III data and discuss it with FDA.

In a Jan. 5 note, WedBush analyst Liana Moussatos said KPI-121 might be approvable in dry eye on the basis of two STRIDE studies given that subanalyses of more severe patients showed a benefit on the symptom endpoint in STRIDE-2, but said it was also possible Kala would need to conduct a third Phase III trial before filing. The analyst pushed her projection of KPI-121 approval in dry eye back several months, from April to September of 2019. She puts the potential peak sales for the dry eye product at $1.9bn by 2027.

After the STRIDE study data were released Jan. 5, Biomedtracker lowered its likelihood of approval for KPI-121 0.25% by three percentage points to 43%, eight percentage points below average for a Phase III dry eye candidate.

Kala expects to reach market first with KPI-121 1% (provisional brand name *Inveltys*) for post-surgical pain and discomfort and hopes to commercialize both eye drop products itself. Kala announced Jan. 5 that the Inveltys NDA had been accepted for review by FDA, with an approval decision by Aug. 25, 2018. Dry eye is seen as the bigger commercial opportunity, Iwicki noted. The company is building a sales force expected to be between 150-200 people to market both products.

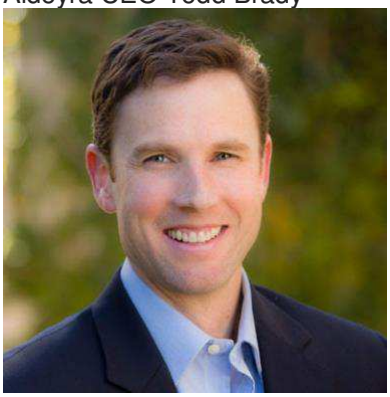
Aldeyra Candidate Shows Potential In Several Signs, Symptoms

Aldeyra is taking an anti-inflammatory approach to dry eye with its reproxalap (ADX-102), and has produced Phase IIa data showing promise for the concept of trapping aldehyde for therapeutic benefit. In September 2017, the Lexington, Mass.-based firm reported that pooled data from a 28-day, 51-patient, dose-ranging study showed significant improvement from baseline across a series of dry eye signs and symptoms, including SANDE (Symptom Assessment in Dry Eye) score, ocular discomfort score, Over Four-Symptom score, the Schirmer test measuring tear volume, tear osmolarity and Lissamine Green ocular surface staining score.

The Phase IIa trial also indicated that reproxalap shows improvements in dry eye signs and symptoms within one week – a potentially important point of differentiation from Restasis and Xiidra – with a clean safety profile and no serious adverse events reported. Aldeyra CEO Todd Brady told *Scrip* that his company was focused on developing novel therapies specifically for the eye (and possibly later addressing non-eye inflammatory indications) and that reproxalap was being advanced simultaneously in dry eye, allergic conjunctivitis and non-infectious anterior uveitis, a rare autoimmune disease of the eye.

Despite a recent setback – not meeting the primary endpoint in a Phase II study in allergic conjunctivitis – Aldeyra is proceeding with a Phase III study in that indication due to its confidence in the aldehyde trap's overall profile. (Also see "Aldeyra's Allergy Drug Misses Endpoint But Company Sees Market Gap" - Scrip, 15 Jun, 2017.) Brady says there is "important overlap" between dry eye and allergic conjunctivitis and estimates that there are tens of millions of patients who have components of both diseases, such as sub-indications like itchy dry eye, allergic dry eye and dry allergic conjunctivitis.

Aldeyra CEO Todd Brady



Source: Aldeyra Therapeutics Inc.

"I think this is the only ocular drug in development for all three of those and probably the only ocular drug in development for both allergic conjunctivitis and dry eye, which are both blockbuster markets," Brady said. This could be vital to reproxalap market prospects, he added, because neither Restasis nor Xiidra has shown efficacy in allergic conjunctivitis.

Brady thinks prescribers will be very interested in a dry eye therapy offering advantages over the two currently marketed drugs, because dry eye is chronic, persistent and disturbing to patients. "I think most physicians and patients would agree that the activity for those two drugs is modest; there are side effects with Restasis and Xiidra causes taste disturbances that are persistent," he noted. "So there is room for novel mechanisms, there's room for better activity and there is room for a better safety profile."

Aldeyra plans to initiate a 225-patient Phase IIb study of reproxalap during the first quarter of 2018, testing 0.1% and 0.25% doses for 12 weeks. Data readout could occur during the second half of the year. In a Sept. 12 note, Laidlaw & Co. analyst Yale Jen said the "robust clinical response across multiple measurements" seen in the Phase IIa study boded well for further development of reproxalap.

"Potential approval might only require success of one sign and symptom endpoint," the analyst wrote. "We also view the rapid drug responses and well differentiated MOA could set ADX-102 apart from all other marketed [dry eye] products."

Founded in 2004, Aldeyra had an initial public offering netting $11.4m in 2014. [See Deal] Since then, however, it has raised roughly $78m more via a PIPE (private investment in public equity) financing and four follow-on public offerings. [See Deal] Brady estimates the biotech's cash will last through 2019, getting it to Phase III data in allergic conjunctivitis and non-infectious anterior uveitis, as well as Phase IIb data in dry eye.

The company's likely direction forward is to partner for the larger dry eye and allergic conjunctivitis indications, while retaining co-promotion rights for uveitis. Brady said Aldeyra had no plans to hire a sales force of about 500, which would be needed for dry eye, but that a rare disease like uveitis would be more manageable to commercialize.

"There are probably about 30 anterior segment specialists in the US who are responsible for the bulk of severe ocular inflammation," he said. "Those people we know, they are enrolling patients for us in Phase III uveitis. That is a co-promotion right that we intend to retain no matter what."

Ocugen Hopes To Show Broader Benefit Than Restasis, Xiidra

Ocugen recently advanced OCU310, its combination of brimonidine, an off-patent vasoconstrictor used to treat glaucoma and ocular hypertension, and an undisclosed steroid, into a Phase II study that is expected to yield data during the first quarter of 2018. CEO Shankar Musunuri told *Scrip* he hopes this trial – using the SANDE test score to measure symptomatic benefit and ocular redness as an endpoint for signs of dry eye – will lead to a pivotal Phase III program for the candidate.

Ocugen CEO Shankar Musunuri

Source: Ocugen Inc.

He noted that the FDA lacked a standard protocol for approving dry eye drugs and that Restasis and Xiidra each were approved partly on the basis of efficacy in different dry eye symptoms. Musunuri believes the questionnaire used for SANDE will yield robust data. In signs of the disease, Ocugen hopes to produce more sophisticated data than some other programs – it will use an Ocular Keratograph to measure patients' ocular redness.

The biotech's two lead programs – the other is OCU300, a brimonidine nano-emulsion formulation for ocular graft-versus-host disease – will both use the 505(b)(2) pathway for approval, and Ocugen hopes to initiate a Phase III trial in dry eye by the third quarter of 2018. Although it is not saying publicly which steroid is incorporated into OCU310, Musunuri said it was an FDA-approved agent with an established safety profile.

Ocugen holds a patent covering a broad method of treatment of dry eye with brimonidine, including combinations and formulations, Musunuri noted. "The molecule is used in glaucoma because it's a good vasoconstrictor," he said. "It's also an alpha2 adrenergic agonist, so it has analgesic properties and immunosuppressive properties as well as inhibiting leukocyte activation."

The biotech asserts that OCU310 will offer advantages over Restasis and Xiidra because it will offer leukocyte immunosuppression and disrupt leukocyte leakage, as well as providing analgesic and vasoconstriction effects. Restasis offers the leukocyte benefits, but not the latter two OCU310 may provide, and Xiidra only disrupts leukocyte leakage. The corticosteroid component of Ocugen's drug will provide an anti-inflammatory benefit.

"We want our product to offer more rapid onset of action, alleviation of ocular pain and photophobia, as well as a rapid reduction in surface swelling and discharge with a safe product," Musunuri said.

Ocugen also believes the safety profiles already demonstrated for both components of the combination product indicate that OCU310 will be safe for longer-term use. Both compounds have been approved for chronic use separately, Musunuri pointed out.

Ocugen thinks it will get to market quicker with OCU300 because ocular GVHD is an orphan indication. It raised a $6m Series A round in 2016 and has enough cash to get both programs through proof-of-concept, leading up to Phase III, Musunuri said. [See Deal] The biotech is agnostic on partnering possibilities, he added, preferring only "whatever will maximize our value."

Lots of assets are in the pipeline, but establishing a new commercial success in the dry eye space will now require competing against a generic version of a well-established rival. The bar has been raised.