

Space set for a sea change

No 'Rest' for DED as blockbuster wannabes jockey for lead

By Marie Powers, Contributing Writer

The hunt is on for a dry eye disease (DED) therapy to replace Allergan plc's blockbuster, Restasis (cyclosporin), which the Dublin-based firm sought to shield behind the protective estate of 27 patents, including six famously assigned in 2017 to the Saint Regis Mohawk Tribe and then licensed back in perpetuity, seeking to prevent their expiry in 2024. (See *BioWorld*, Sept. 20, 2017, and Feb. 27, 2018.)

Generics manufacturers are waiting in the wings after the U.S. Federal Circuit in November upheld a Patent Trial and Appeal Board decision that invalidated the six patents for obviousness. The Federal Circuit had ruled against tribal sovereign immunity a few months earlier.

The heir apparent to Restasis, at least for now, appears to be the small-molecule LFA1/ICAM-1 antagonist Xiidra (lifitegrast). Shire plc, of Dublin, advanced the FDA-approved integrin-targeted anti-inflammatory – the first developed specifically for ocular use – to market after acquiring developer Sarcode Bioscience Inc. in March 2013. Shire first had to overcome a complete response letter requesting additional data from a phase III study that, fortuitously, was underway. (See *BioWorld*, Oct. 20, 2015.)

Xiidra contributed \$259 million in revenues to Shire's bottom line during 2017, its first full year on the market, with sales growing to \$388 million in 2018, and the five-year consensus forecast is north of \$1 billion. Last month, Novartis AG, of Basel, Switzerland, placed a big bet on that outcome, picking up the drug from debt-laden Takeda Pharmaceutical Co. Ltd. in a potential \$5.3 billion deal. Takeda swallowed Shire last year for \$62 billion. (See *BioWorld*, May 9, 2018, and May 15, 2019.)

"We've been building out our ophthalmology portfolio, making sure that we're stronger in forward launches to come," Paul Hudson, CEO of Novartis Pharmaceuticals, told analysts in discussing the deal. "We have a very impressive position in ophthalmology worldwide and in particular in the U.S. [Xiidra] is a perfect strategic fit for us."

Xiidra, he added, "as the only prescription treatment for both signs and symptoms" of DED, "is absolutely out on its own, and it is not a guarantee that anybody will be able to follow." The agent was additionally de-risked by its sales trajectory, he said, citing a "massive" unmet need in DED, with more than 34 million patients in the U.S. alone, more than half already diagnosed. Consequently, the up-front payment of \$3.4 billion

– financed with cash on hand – was "a very sensible level," according to Hudson, "based on the fact that we think we can accelerate the medicine."

Jefferies Group LLC analysts came away believers after hosting a fireside chat with Fabrice Chouraqui, president of Novartis Pharmaceuticals U.S., earlier this month. Peter Welford and team proclaimed themselves "enthusiastic on key growth drivers," including the Xiidra acquisition, pointing to the benefits of Novartis' sales and marketing strategy as well as a reported \$500 million tax synergy. "Management assumes payers will step patients through competitor Restasis, which could soon be genericized, but notes short average durations on this drug," the Jefferies analysts observed in their takeaway.

'Xiidra usage is likely to remain contained to most severe' patients

The size of the Xiidra deal has other analysts abuzz about the ophthalmic space and DED, in particular. Anti-inflammatories approved to treat DED are low-risk but their side effects are poorly tolerated by some patients: Restasis can cause a burning sensation in the eyes while Xiidra can cause an unpleasant taste. The biggest problem with both medications, however, is that they simply don't work for many individuals.

Research conducted by the American Academy of Ophthalmology suggests that fewer individuals diagnosed with DED present with dryness due to lack of sufficient tears than with inflammation on the ocular surface or dysfunctional tear composition – lacrimal fluid that is too salty, insufficient in volume or displaying increased osmolarity. Correspondingly, treatment for DED isn't a one-size-fits-all affair. Lifestyle modifications, including environmental strategies and dietary changes, often are recommended. Pharmacotherapy traditionally starts with artificial tears products, which vary in viscosity, composition and formulation, before turning to drug therapies that include mucin production enhancers and anti-inflammatory agents. (See *BioWorld Insight*, July 30, 2018.)

Dry eye, technically xerophthalmia, also is increasing in prevalence, in part, due to the growing ranks of cancer survivors, who often develop chronic DED as a side effect of their oncology drug regimens. The size of the space powered Restasis through more than a decade of rising sales. The agent topped \$1 billion in sales in 2014 and peaked in 2016 at about \$1.5 billion. Last year, Allergan reported Restasis sales of approximately \$1.3 billion, representing a year-over-year

decline of 14.4%. With the loss of patent protection, the five-year consensus sales forecast is just \$40.9 million, according to Cortellis Competitive Intelligence.

Ironically, the list of non-over-the-counter DED drug contenders has been slim, at least in the U.S. In addition to Restasis and Xiidra, only Sun Ophthalmics, a unit of Sun Pharmaceuticals Industries Ltd., of Mumbai, India, has a contender on the market following last year's approval and launch of Cequa (formerly OTX-101), a nanomicellar formulation of cyclosporin (cyclosporine A, 0.09%). The company acquired the rights in 2016 from Auvex Therapeutics Management LLLP, of St. Thomas, U.S. Virgin Islands.

Kala Pharmaceuticals Inc. may join that list in short order. In January, the Waltham, Mass.-based company launched Inveltys (loteprednol etabonate, formerly KPI-121) 1% following an August 2018 FDA nod for postoperative inflammation and pain following ocular surgery. Even before the launch, the agency accepted the company's NDA for KPI-121 0.25% to treat DED, setting a PDUFA date of Aug. 15, although the confirmatory STRIDE 3 trial is not expected to report until the fourth quarter. In an earnings note on Kala last month, H.C. Wainwright analyst Raghuram Selvaraju pointed out that, based on the approval history of Xiidra, "we believe the company could receive a complete response letter from the FDA on the PDUFA date requesting additional clinical trial data. Kala could then provide the STRIDE 3 data in a resubmission, which may occur in early 2020, followed by a six-month review period. In our view, KPI-121 0.25% may obtain regulatory approval in 2H20."

Like Selvaraju, the prospect left Jefferies analyst Biren Amin unfazed.

"Though it's unlikely FDA approves without STRIDE-3 data," Amin wrote in an earnings note, "[management] is seeking [the] fastest regulatory path by filing [an] NDA ahead of STRIDE-3, which would allow second submission and approval within [six months] and set up a late '20 launch." Moreover, the Kala team expects "no impact" on the market opportunity with Xiidra in the hands of Novartis, he added, since "Xiidra usage is likely to remain contained to most severe, chronic [patients] whereas '121 0.25% can address [patients] with acute, episodic flares."

'A paradigm shift in the treatment of ophthalmic disease'

Going forward, the DED space is set for a sea change. A late-stage pipeline with diverse mechanisms of action boasts nearly a dozen candidates in phase III development and twice that number in phase II. (See charts, [page 3](#).)

Aldeyra Therapeutics Inc. is one to watch. The Lexington, Mass.-based firm is advancing reproxalap (ADX-102; formerly NS-2), a reactive aldehyde species inhibitor formulated using Captisol technology licensed from Ligand Pharmaceuticals Inc., to treat acute noninfectious anterior uveitis and allergic conjunctivitis (AC) along with DED. Last year, Aldeyra reported that its randomized, parallel-group, multicenter, double-masked phase IIb study in 300 individuals with DED study showed that, relative to vehicle, individuals treated with the 0.25% concentration had statistically significant and clinically relevant reductions in the Four-Symptom Ocular Dryness Score ($p < 0.05$) and the Overall Ocular Discomfort Symptom Score ($p < 0.05$).

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Paul Hudson
CEO, Novartis Pharmaceuticals

Symptom improvement greater than that of vehicle turned up consistently across all measures, and researchers found activity as early as two weeks, the first assessment after the start of therapy.

The findings gave Aldeyra the confidence to float the idea of a dual NDA submission in DED and AC, as "there is published literature supporting the prominence of co-morbidities between the two conditions," David McMullin, senior vice president of corporate development and strategy, told *BioWorld* at the time. (See *BioWorld*, Sept. 27, 2018.)

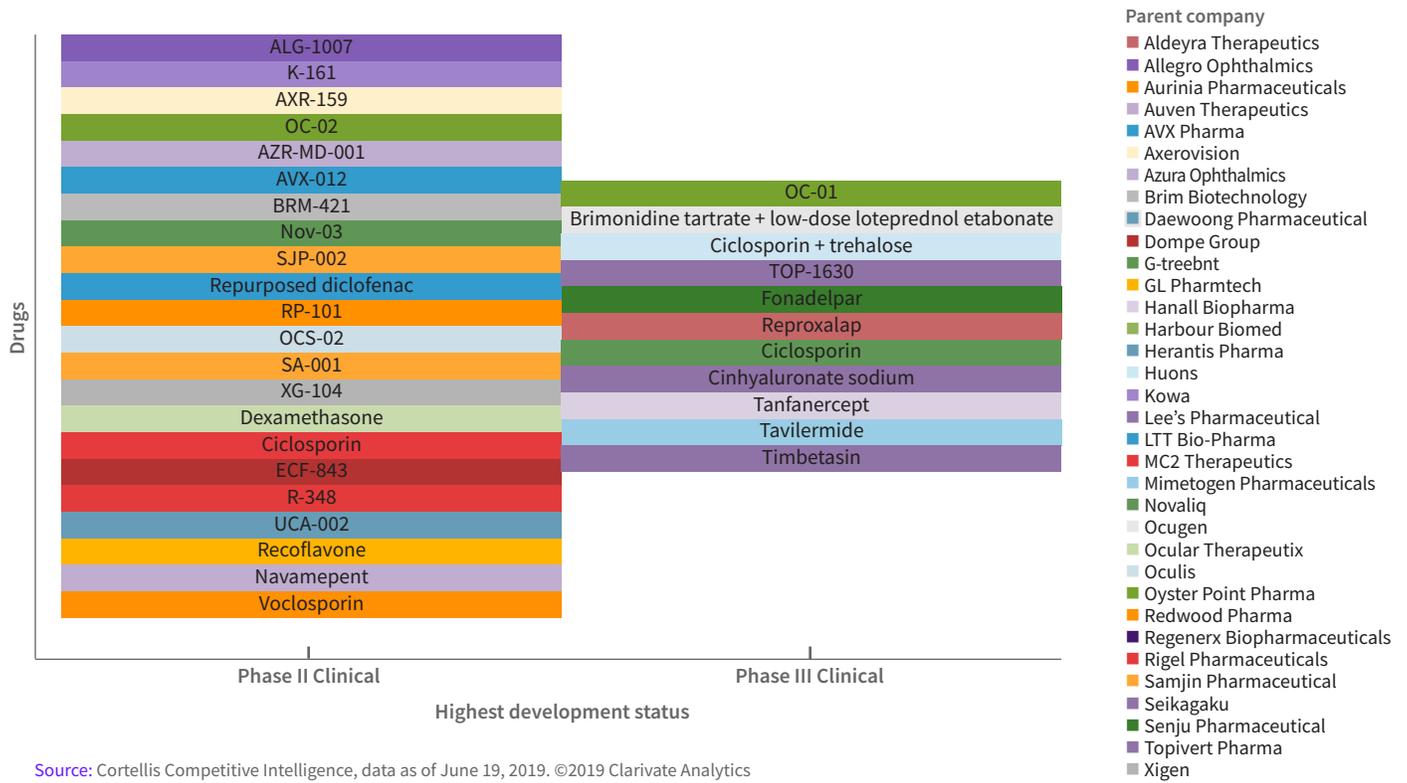
Those deliberations were strengthened in March with top-line data from a reproxalap phase III AC study that showed two concentrations drove statistically significant reductions in ocular itching vs. placebo. The 0.25% concentration is the same that's under evaluation in the randomized, double-blind, vehicle-controlled, parallel-group phase III RENEW test of the drug in DED, which in April began enrolling an estimated 400 participants in the U.S. Co-primary endpoints are ocular dryness symptom score and fluorescein nasal region staining, with data expected in the second quarter of 2020. (See *BioWorld*, March 27, 2019.)

"No drug is specifically approved for the treatment of both dry eye disease and allergic conjunctivitis and thus reproxalap, if approved, may represent a paradigm shift in the treatment of ophthalmic disease as a single therapeutic approach applicable to ocular discomfort and irritation that arises from inflammation," Todd Brady, Aldeyra's president and CEO, told analysts on a call to disclose the findings.

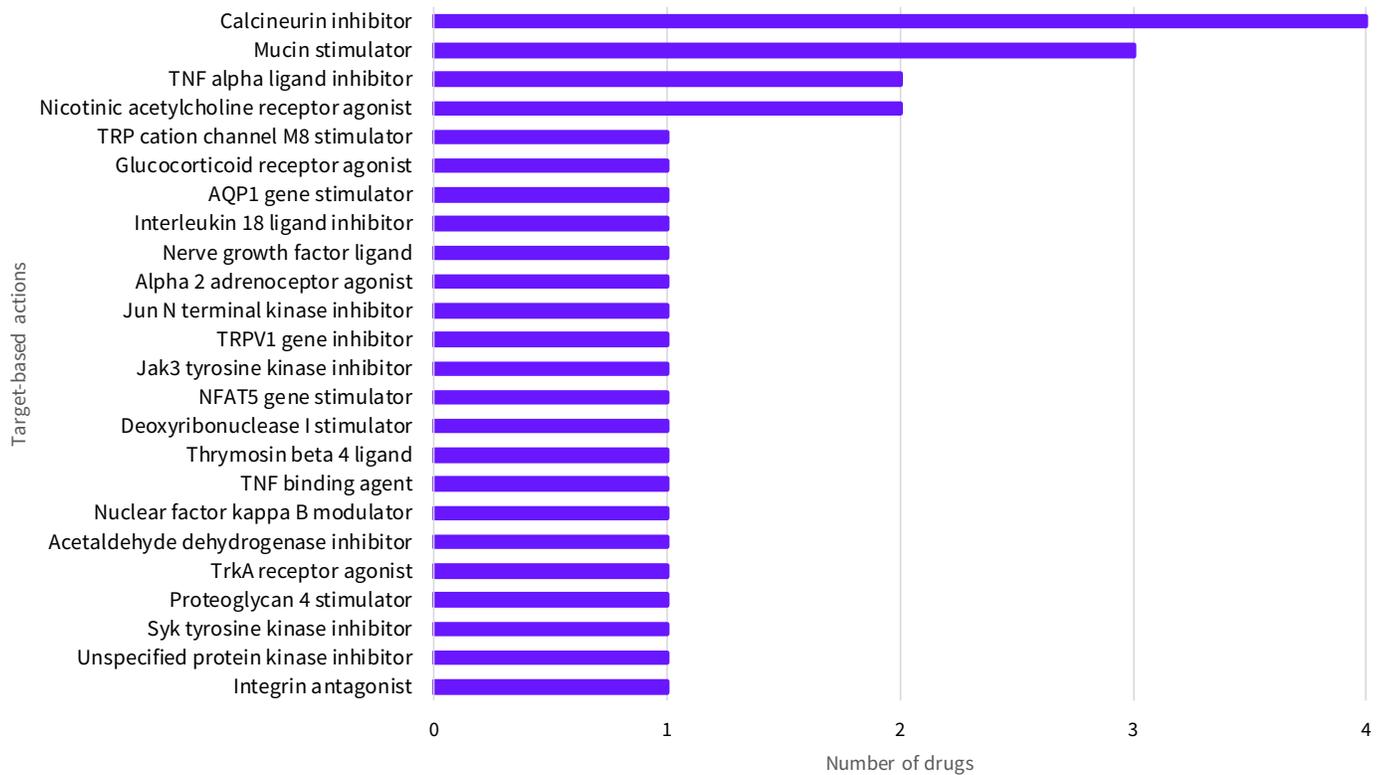
Aldeyra expects to confirm clinical requirements for regulatory submissions in AC – potentially concurrent with DED – in the second half of this year. The company's shares (NASDAQ:ALDX) hit a 52-week high of \$16.70 in September 2018 following the DED findings and spiked again to \$12.79 on the AC data in March but on June 14 hit a one-year low of \$6.34.

Another contender is RGN-259, the subject of the ARISE-3 trial by Regentree LLC, of Princeton, N.J., a joint venture of Gtreebnt Co. Ltd and Regenerx Biopharmaceuticals Inc. The phase III study is comparing the safety and efficacy of the 0.1% formulation of RGN-259, a preservative-free eye drop formulation of synthetic timbetasin (thymosin beta-4), to placebo in 700 participants. Data are expected in mid-2020. Design of the trial is based on findings from the phase III ARISE-1 and ARISE-2 trials, which enrolled approximately 300 and 600 participants, respectively, at a single U.S. site. ARISE-2 showed a number of statistically significant improvements in both signs and symptoms with 0.1% RGN-259 vs. placebo, along with good safety, comfort and tolerability profiles, including a statistically significant reduction in the ocular

Phase II/III dry eye disease candidates, by company



Mechanisms of action for dry eye disease candidates in phase II/III development



discomfort symptom score in the treated group vs. placebo at day 15 ($p=0.0149$). But ARISE-2 did not duplicate the results of the ARISE-1 phase III, which Wainwright's Selvaraju attributed at the time to a more diverse patient population.

In April 2018, the FDA requested an additional phase III trial to evaluate efficacy in a larger population, but the agency accepted safety data from ARISE-1 and ARISE-2, said no additional nonclinical efficacy or safety studies were required and deemed the company's chemistry and manufacturing control plans for the drug substance and product complete and acceptable for NDA submission. ARISE-3 is evaluating corneal fluorescein staining and ocular discomfort severity at day 15 as primary endpoints, according to Cortellis Clinical Trials Intelligence. Meanwhile, licensee Lee's Pharmaceutical Holdings Ltd., of Hong Kong, is advancing the DED candidate in China.

Private biopharmas generating much of the phase III DED activity

Much of the phase III action has emerged at privately held concerns. Ocugen Inc., of Malvern, Pa., has advanced the alpha-2 adrenergic agonist, OCU-310, a combination of brimonidine tartrate 0.2% and low-dose loteprednol etabonate, into a phase III program. In April, Ocugen said it completed the first randomized, placebo-controlled, double-masked trial, which enrolled 240 participants across 25 centers, and was awaiting the full dataset. In a placebo-controlled phase II trial completed last year, OCU-310 showed meaningful improvements across endpoints related to signs and symptoms of DED. (See *BioWorld*, July 3, 2018.)

In the meantime, Ocugen struck a deal this year to merge with publicly held Histogenics Corp. Once the transaction closes, expected by the end of the third quarter, Ocugen, as the surviving entity, will gain a Nasdaq listing as OCGN. (See *BioWorld*, April 9, 2019.)

After phase IIb success with nicotine acetylcholine receptor (nAChR) agonist OC-01, Oyster Point Pharma Inc. this year opened the phase II/III long-term follow-up ONSET trial to evaluate safety and efficacy of the candidate six and 12 months following treatment in ONSET-1. The study is expected to read out in the fourth quarter.

ONSET-1 showed a statistically significant improvement in the prespecified primary endpoint of tear production as measured by Schirmer's score at day 28, with mean change in score values of 11.4 mm, 11.8 mm and 10 mm at 0.2%, 0.1% and 0.02% doses, respectively, with 3.2 mm for vehicle control. Prespecified secondary endpoints were also met. In February, the Princeton, N.J.-based company landed a \$93 million series B financing to support phase III development.

Oyster Point has a second selective nAChR agonist, OC-02, in phase II development. In general, both compounds leverage the trigeminal parasympathetic pathway to activate the glands that comprise the lacrimal functional unit and promote tear film production, delivered as a nasal spray.

In February, Topivert Pharma Ltd., of London, initiated a phase II/III study of TOP-1630, a narrow spectrum kinase inhibitor, in individuals with moderate to severe DED. The randomized,

parallel assignment, quadruple, double-masked THEIA-1 study is expected to enroll 200 participants across four U.S. centers to evaluate the 0.1% ophthalmic solution vs. placebo. Co-primary endpoints include assessments of ocular grittiness severity and ocular surface staining. Top-line data are expected at the end of the third quarter.

Mimetogen Pharmaceuticals Inc. is advancing tavilermide (MIM-D3), a small-molecule nerve growth factor peptidomimetic, as a tropomyosin-related kinase A receptor agonist that is also a mucin secretagogue, in a 1% ophthalmic solution. The Montreal-based company is going it alone after Allergan pulled out of a 2015 licensing deal. In March, Mimetogen opened a phase III U.S. study expected to enroll 600 participants, with co-primary endpoints of change from baseline in eye dryness score and total corneal fluorescein staining. Data are expected in the second quarter of next year.

And partners Hanall Biopharma Co. Ltd. and Daewoong Pharmaceutical Co. Ltd., both of Seoul, advanced tanfanercept (HL-036) into the randomized, double-masked, placebo-controlled phase III VELOS-2 study, which is expected to enroll about 630 participants across three U.S. sites. Data are due around year-end, with corneal fluorescein staining and ocular discomfort severity also as co-primary endpoints. The etanercept biobetter, which acts as a TNF alpha blocker, consists of a fragment of the p55 TNF receptor I fused to an antibody fragment. The agent was the subject of a 2017 licensing agreement with Shanghai-based Harbour Biomed Therapeutics Ltd., which is developing tanfanercept in China. (See *BioWorld*, Sept. 14, 2017.)

Others with phase III candidates include Senju Pharmaceutical Co. Ltd., of Osaka, Japan, with fonadelpar (SJP-0035) and Novaliq GmbH, of Heidelberg, Germany, with CycloSol (formerly CycloSol), a cyclosporin A formulation using the company's semifluorinated Eyesol ophthalmic drug delivery technology.

Not all of the phase III candidates are seeking entry into the U.S. market. Huons Co. Ltd., which markets a ciclosporin nanoemulsion product for DED in South Korea, also has a nanocomposite of ciclosporin and trehalose in development for that market. Japan's Seikagaku Corp. is developing a modified hyaluronate cinhyaluronate sodium, dubbed SI-614, from glycosaminoglycan modulators but is seeking to out-license the agent in the U.S.

Sylentis SA, of Madrid, a subsidiary of Pharmamar SA, which is advancing tivanisiran initially in the EU, had mixed results this year with the RNAi-based inhibitor of transient receptor potential cation channel 1, a ligand-gated ion channel that mediates the sensation of pain and burning and plays a role in thermoregulation. Its Helix study, which recruited 330 individuals with DED and daily symptoms for at least six months, showed improvements in both change from baseline in total corneal fluorescein staining and in pain score from baseline, but the effects did not outperform those of vehicle. Tivanisiran did, however, show a statistically significant improvement ($p=0.035$) over the comparator in reducing central corneal staining and improved the quality of tears by boosting production of mucin by 125% vs. the comparator.

The company planned to present data to regulators during the second quarter to define a regulatory strategy in DED. (See *BioWorld*, Feb. 1, 2019.)

Unlocking value in DED through 'cost-efficient investment'

More excitement may ensue as phase II studies read out. Aurinia Pharmaceuticals Inc., of Victoria, British Columbia, has generated buzz with its once-daily, nanomicellar 0.2% formulation of the calcineurin inhibitor voclosporin (VOS). In January, Aurinia reported top-line results of a 100-patient, four-week, exploratory phase IIa head-to-head study vs. Restasis. The company elected to choose ocular tolerability, measured by change in drop discomfort one minute following instillation, as the primary endpoint, on the basis that the endpoint would most likely demonstrate clear separation from the market leader even in a smaller, short-duration study. That proved not to be the case, however; the study showed no statistical difference between the agents on the primary endpoint.

Newly named CEO Peter Greenleaf nevertheless remained upbeat on the company's first-quarter earnings call in May, maintaining that Aurinia was finalizing plans to initiate a phase II/III study in DED late this year that will encompass "certain critical regulatory requirements that the FDA has traditionally required" for approval in the indication, including dose optimization and comparisons against vehicle.

SVB Leerink LLC's Joseph Schwartz was satisfied with that explanation, observing in an earnings report that, despite approved DED agents, "[management] is committed to

unlocking VOS' value in [dry eye syndrome] through a cost-efficient investment. Longer term, VOS falling outside of AUPH's core expertise in renal indications may lead to a meaningful nondilutive financing for the company."

First, the company must contend with an ongoing proxy fight by its largest shareholder, ILJIN SNT Co. Ltd., of Seoul, South Korea, which is seeking to install three independent directors on Aurinia's eight-member board. Last week, the institutional proxy advisory firms Institutional Shareholder Services Inc. and Glass Lewis & Co. recommended that Aurinia shareholders vote to support the company's nominees prior to this Wednesday's shareholder meeting. In a first take, H.C. Wainwright analyst Ed Arce affirmed a "buy" rating on the stock as "we continue to believe ILJIN's claims are poorly substantiated." On Thursday, Aurinia's shares (NASDAQ:AUPH) closed at \$6.17, down 19 cents.

Oculis SA is another phase II player to watch in DED. In January, the Lausanne, Switzerland-based company added an extension of CHF15.5 million (US\$15.7 million) to its CHF20 million series B round as it in-licensed LME-636, an anti-TNF-alpha candidate, from Novartis. LME-636, since renamed OCS-02, is based on a single-chain antibody fragment designed for topical delivery. The asset came to Novartis through its acquisition of the Alcon eye care business and was evaluated in two placebo-controlled U.S. phase II trials run by the Novartis Institute of Biomedical Research. Oculis is conducting additional formulation work before resuming development, first in DED and then in uveitis. (See *BioWorld*, Jan. 7, 2019.) ♦