

The American Academy of Ophthalmology Responds to Meaningful Use Rules

The US Department of Health and Human Services released its final rules for changes to stages 1 and 2 of the electronic health record incentive program, stage 3 requirements, and the 2015 electronic health record certification criteria. In response, the American Academy of Ophthalmology (AAO) released the following statement and information.

"The final rule provides physicians much of the critical relief that the Academy has been fighting for, however it's far from a perfect solution," Michael X. Repka, MD, MBA, the AAO's medical director of government affairs, said in a news release. "For physicians who have been waiting to begin reporting based on relief in the rule, the rule's delayed timing makes it impossible to be successful in the program because there are fewer than 90 days left in 2015. The Academy will continue to demand accommodations for these providers."

What is the good news?

- Flexibility. Physicians have a shortened reporting period this year of 90 days.
- Better opportunity for success. These revisions are expected to help physicians avoid a 3% penalty.
- Online portal measures. This rule relaxed the requirements for encouraging patients to use online portals. Now, instead of 5% of their patients, physicians only need one patient to view, download, and transmit his or her electronic health information.

What is not so good about this rule?

- The timing. Shortening the reporting period to 90 days only helps if there are more than 90 days left in the 2015 calendar year, which there are not.
- The shortened reporting period is not permanent. The 90-day period is only for 2015.
- The Centers for Medicare & Medicaid Services finalized the stage 3 rule. Across medicine and within

Congress, the belief is that the only way to preserve the overall goals of the meaningful use program would have been to pause rulemaking for stage 3. No other action can ensure that the meaningful use program is aligned with the changes stemming from the Medicare Access and CHIP Reauthorization Act of 2015. A pause was also the only chance to completely understand the impact of stages 1 and 2.

What do ophthalmologists need to know?

Ophthalmologists should become familiar with this rule immediately. The AAO has an updated attestation guide for this rule. Members can access it at aao.org/practice-management/electronic-health-records/meaningful-use/attestation. If you need assistance, you can contact a group of Academy experts who are familiar with meaningful use requirements at ehinfo@aao.org.

What is next?

The Academy has endorsed Congress' pursuit of a permanent solution. AAO members can send a letter to their member of Congress to urge support for the FLEX-IT 2 Act. This legislation permanently shortens the reporting period, provides a hardship exception, and pauses stage 3.

The Academy will continue to work with a coalition including the American Medical Association and other physicians and hospital groups to ask for accommodations to help all providers affected by the agency's delayed rulemaking.

The AAO is demanding that the Centers for Medicare & Medicaid Services act immediately to provide relief, including the creation of a new hardship exception category for eligible professionals affected by the delayed rulemaking that would allow physicians to avoid penalties associated with the 2015 reporting year. The Academy is also asking that the timeline be modified to allow the 2015 reporting period to extend into the 2016 calendar year.

Ocular Therapeutix Reports Topline Results of Phase 2b Glaucoma Clinical Trial

Ocular Therapeutix announced topline results through 90 days of therapy from its phase 2b clinical trial of OTX-TP (sustained-release travoprost) for the treatment of

glaucoma and ocular hypertension, according to a company news release.

OTX-TP is administered by a physician as an intracanalicular depot through the punctum and is designed to deliver travoprost to the ocular surface for up to 90 days. In the phase 2b trial, the duration of effect, as measured by the clinically meaningful reduction of IOP in the range of 4.5 to 5.7 mm Hg, was observed out to 90 days with sustained-

September/October 2015 Online Survey Results

For the visual field testing of patients with advanced glaucoma, which testing strategy do you generally use?

A standard 24-2 testing strategy	21.21%
A 24-2 testing strategy with an enlarged stimulus	15.15%
A 10-2 testing strategy	60.61%
None of the above	3.03%

release OTX-TP. The company said this level of IOP lowering was comparable to that seen in the treatment group with the same drug release rate in the phase 2a clinical trial of OTX-TP. In the 2b trial, the patient group receiving timolol as a comparator drug in the presence of a placebo depot achieved IOP-lowering results that were greater than expected, based on results reported in the peer-reviewed literature. However, as previously reported, the trial was not powered to detect statistically significant differences in IOP lowering between the patient groups.

No hyperemia-related adverse events were noted in any of the patients treated with OTX-TP, and there have been no serious adverse events observed to date in the phase 2b trial. Adverse events were generally similar in frequency across the treatment groups. A complete analysis of all safety data is pending the study's completion.

The prospective, multicenter, randomized, double-masked, double-dummy, parallel-arm, active controlled study enrolled 73 patients at 11 clinical sites in the United States to assess the efficacy and safety of OTX-TP as compared to timolol. The study was designed to inform the further clinical development for OTX-TP and was not powered to show statistical significance between study groups. Study efficacy measures included differences in the mean IOP change between the treatment groups from baseline at multiple time points throughout the study. Additional objectives included depot retention, visualization, and replacement if required, duration for washout to achieve a stable baseline IOP, and a comparison of safety profile.

The timolol group was observed to have IOP lowering of 6.4 to 7.6 mm Hg (mean, 7 mm Hg) compared with baseline, which was higher than expected, possibly due to enhanced residence time of the drug on the ocular surface due to occlusion of the punctum by the placebo vehicle depot. The average IOP lowering seen in four published studies using timolol was 6.2 mm Hg. On day 60, which was the primary efficacy measure, the OTX-TP group had an IOP-lowering effect of 4.8 mm Hg, compared with

6.4 mm Hg for the timolol arm. On day 90, which was a secondary efficacy measure, the OTX-TP group had an IOP-lowering effect of 5.2 mm Hg, compared with 7.3 mm Hg in the timolol arm.

The phase 2b interim results are reported on all patients observed through a 90-day duration. Complete results on safety and efficacy through the end of the study are expected to be available in the first quarter of 2016.

Depots were retained in 91% of patients at day 60 and 88% on day 75, when evaluating all patients completing the study through its 90-day duration. Retention was 48% at day 90, reflecting the corresponding absorption and clearance of the depots with the duration of drug release.

All patients were able to visualize the presence of the depots throughout the trial and ask for replacement depots if and when required. All but two patients treated with OTX-TP were able to successfully receive a replacement product when their depots were lost anytime before day 90.

Baseline (washout) evaluations for IOP were conducted 4 and 5 weeks after screening. It was seen that baseline IOP continued to drop by 1 mm Hg for the OTX-TP group and 0.61 mm Hg for the timolol group from week 4 to week 5, signaling the potential need for a longer washout duration in future studies.

The company said it plans to investigate in nonsignificant risk studies whether or not the presence of the high-retaining placebo depots is enhancing the effect of timolol, as this has been reported in the literature. The company also plans to discuss potential clinical study designs with the FDA to potentially minimize this effect and better reflect real-world usage.

Allergan Exec on Dry Eye Drug Market: "More Than Enough to Go Around"

During a conference call with investors to discuss third quarter earnings on November 4, Allergan executives were asked what their outlook is for Restasis (cyclosporine ophthalmic emulsion 0.05%), given the recent positive data for Shire's dry eye drug candidate lifitegrast, which, if approved, would serve as the first pharmacological competitor to Restasis.

"I don't believe this is going to be a fight to the death between Shire and Allergan," said Bill Meury, president, branded pharma, at Allergan. "I said before that the gap between the prevalent (dry eye) population and the prescription-treated population is enormous. It's larger than it is in most categories. The importance of dry eye disease is clear and it's getting more and more attention because of the impact it has on quality of life, the impact that it could have on vision, and positive postop outcomes."

Last week, Shire announced topline results from OPUS-3,

a phase 3 efficacy and safety study of lifitegrast. In the trial, lifitegrast met the single primary endpoint for patient-reported symptoms of eye dryness (mean change in eye dryness score from baseline to week 12 [$P = .0007$]), and met the secondary endpoints of symptom improvement at days 14 and 42 ($P < .0001$ for both endpoints).

In October, the FDA formally declined Shire's dry eye disease drug lifitegrast. The government agency requested further clinical tests along with more information about product quality. Shire says the OPUS-3 data puts the drug candidate back on track for a commercial launch in 2016.

Mr. Meury said the dry eye disease market is large enough to support both drugs.

"When you look at the data set between the drugs I would simply say that we will have to see how lifitegrast holds up in the real world," Mr. Meury said. There's no doubt eye care professionals are going to try something new, but I believe long-term, this category has the potential to double, so there's more than enough to go around."

Research and consulting firm GlobalData concurs. In a recent report,¹ GlobalData stated that the global treatment market for dry eye will more than double in value from about \$2.2 billion in 2014 to an estimated \$4.6 billion by 2024, representing a compound annual growth rate of 7.9%.

The growth will be driven primarily by the introduction of novel drugs, most notably lifitegrast, the report stated.

Catherine Daly, PhD, GlobalData's senior analyst covering neurology and ophthalmology, stated in a news release that the paucity of dry eye syndrome treatments in the United States and European markets will allow Shire to secure strong uptake and a sizable market share for lifitegrast.

"GlobalData expects that lifitegrast, which is anticipated to launch in the US in late 2016, will eventually reach peak sales of \$1 billion across the 9 (major markets), earning the drug blockbuster status," Ms. Daly said. "Furthermore, Allergan's blockbuster dry eye syndrome drug, Restasis, which generated an estimated \$1.33 billion in US sales in 2014, is expected to launch in the European markets during the forecast period and will secure a sizable patient share."

Allergan is also investing in the potential of an additional dry eye therapy in late-stage development. This week, the company announced that it has entered into an exclusive licensing agreement with Mimetogen Pharmaceuticals to develop and commercialize tavilermide (MIM-D3), a topical formulation of a novel small molecule TrkA agonist for the treatment of dry eye disease.

Under the terms of the agreement, Allergan will make an upfront payment of \$50 million to Mimetogen and will fund phase 3 development of tavilermide. Mimetogen will additionally be entitled to receive potential milestone payments and royalties based on commercialization of the product.

Tavilermide is a small cyclic peptidomimetic of NGF, a naturally occurring protein in the eye responsible for the maintenance of corneal nerves and epithelium. Tavilermide

is differentiated from other investigational therapies in dry eye disease, because it induces the production of mucin, a naturally occurring component of the tear film, and works upstream prior to inflammation, according to Allergan. Tavilermide is currently being evaluated in two multicenter phase 3 clinical studies in the United States.

Ms. Daly of GlobalData said that Mimetogen's MIM-D3, Mitotech's Visomitin, and RegeneRx's RGN-259 are also expected to see strong sales growth by 2024, as these first-in-class drugs all have different therapeutic benefits to offer patients with dry eye syndrome.

In addition, Mr. Meury said during the conference call that Allergan is going to launch a multidose, preservative-free form of Restasis in the second half of 2016. The new formulation will be more convenient for patients, he added, because it will be easier to administer.

1. GlobalData. PharmaPoint: Dry Eye Syndrome - Global Drug Forecast and Market Assessment to 2024. November 2015. www.globaldata.com. Accessed November 9, 2015.

Inotek Pharmaceuticals Initiates Dosing of MATRx-1 for Phase 3 Trial of Trabodenoson

Inotek Pharmaceuticals has commenced dosing in MATRx-1, the company's first pivotal phase 3 trial of trabodenoson for the treatment of glaucoma. Trabodenoson, Inotek's lead clinical candidate, is a first-in-class selective adenosine mimetic under investigation for the reduction of IOP, according to a news release.

MATRx-1 is a phase 3 randomized, double-masked, placebo-controlled trial of trabodenoson in approximately 335 patients diagnosed with primary open-angle glaucoma or ocular hypertension. The trial will assess the efficacy, safety, and tolerability of trabodenoson over 3 months. The primary endpoint will be the reduction of IOP as compared to the placebo. In addition, the study will contain a timolol 0.5% arm to validate the sensitivity of the patient population. IOP will be measured at four time points during the day, 8 AM, 10 AM, 12 PM, and 4 PM, on days 14, 28, 42, and 84. Three doses of trabodenoson will be administered: 1 mg once daily, 1.5 mg twice daily, and 2 mg once daily. These doses were selected to assess efficacy in IOP lowering, while maintaining the tolerability and safety profile observed in phase 2 trials.

The trial will enroll patients with IOPs greater than or equal to 24 mm Hg and less than or equal to 34 mm Hg, which reportedly represents the patients most likely to receive treatment for glaucoma or ocular hypertension. Inotek said it expects MATRx-1 to be complete in 2016, with topline results anticipated in the fourth quarter of 2016.

"Based on the encouraging phase 2 results as well as guidance from the [FDA], our team has formalized plans for

our phase 3 program to support a new drug application for trabodenoson in glaucoma,” Rudolf Baumgartner, MD, chief medical officer of Inotek, said in a news release. “If approved, trabodenoson—with its potential for once-daily dosing and a mechanism that may complement currently available glaucoma medications—has potential as a valuable treatment option for physicians managing the IOP of patients with this disease.”

“Patients suffering from glaucoma need new therapies that are both efficacious and well tolerated,” William McVicar, PhD, executive vice president and chief scientific officer of Inotek, said in a news release. “Trabodenoson was developed with the objective of restoring the natural pressure-regulating process that occurs in the healthy eye, and thus lowering IOP. The compound specifically targets the adenosine A1 receptor, one of four known receptors for this naturally occurring purinergic regulator. Stimulation of the A1 receptor on human trabecular meshwork cells in culture releases proteases, which can digest and remove hydrolyzed proteins that can clog the trabecular meshwork, obstructing the eye’s drainage system.”

Extended-Release Formulation of Travoprost Shows Potential for Glaucoma

Envisia Therapeutics reported results from its first clinical trial of the company’s lead product candidate, ENV515 (travoprost XR). According to a news release, in this phase 2a trial, ENV515 achieved its primary efficacy endpoint by demonstrating a statistically significant and clinically meaningful reduction in IOP, with results comparable to topical once-daily Travatan Z (travoprost ophthalmic solution; Alcon).

ENV515 is engineered as a proprietary, fully biodegradable PRINT (particle replication in nonwetting templates) travoprost formulation that could offer a sustained reduction in IOP for more than 6 months after a single dose. The company said that, if successful, one to two injections of ENV515 a year in the doctor’s office could satisfactorily control the IOP in most patients without the need for additional eye drops.

The ENV515 phase 2a clinical trial was designed as an open-label, 28-day dose-ranging study that enrolled 21 glaucoma patients at sites within the United States to assess the initial efficacy and tolerability of ENV515. Administered as a single dose, ENV515 achieved its primary efficacy endpoint of a change from baseline in diurnal IOP on day 25 by identifying a dose group (-6.7 mm Hg or -28% , $P < .001$, $n = 10$) that is comparable to once-daily travoprost ophthalmic solution (-6.6 mm Hg or -28% , $n = 21$) administered to the nonstudy eye. The most common adverse event was early-onset transient hyperemia related to the dosing procedure.

Based on these results, Envisia has chosen to advance

ENV515 into a 12-month study that is designed to evaluate the long-term IOP-lowering effect of ENV515, which in preclinical studies demonstrated up to 8 months of IOP-lowering effect after a single dose.

Transcend Medical Submits Final Module of the Premarket Approval Application for the CyPass Micro-Stent

Transcend Medical submitted the final module of the company’s premarket approval application for the CyPass Micro-Stent to the FDA, according to a news release.

The CyPass Micro-Stent is an implant for microinvasive glaucoma surgery (MIGS) designed to reduce IOP in patients with primary open-angle glaucoma. The final module includes 2-year patient follow-up data from the COMPASS pivotal clinical trial, in which more than 500 patients at over 20 US sites were enrolled. According to the company, COMPASS is the largest completed randomized, controlled trial focused on MIGS. In the study, the CyPass Micro-Stent demonstrated superiority over the control by achieving both primary and secondary endpoints at 1 and 2 years.

“We are very pleased to have attained this important milestone and have the CyPass Micro-Stent be the next MIGS technology submitted to [the] FDA for premarket approval,” Brian Walsh, president and CEO of Transcend Medical, said in the news release. “With the robust results from the COMPASS study, we believe the CyPass technology can provide a compelling treatment option for mild-to-moderate glaucoma patients undergoing cataract surgery.”

Clearside Biomedical Completes Enrollment in Phase 2 Clinical Trial of CLS-TA Using Suprachoroidal Space

Clearside Biomedical completed enrollment in the company’s phase 2 clinical trial (Dogwood) of CLS-TA, Clearside’s proprietary form of triamcinolone acetate, using the suprachoroidal space (SCS) for drug administration for the treatment of macular edema associated with noninfectious uveitis, according to a news release. The company said it remains on track to report topline phase 2 CLS-TA data by the end of 2015.

The Dogwood trial is the first masked, randomized trial conducted in humans in which the drug is administered through the SCS, according to Clearside Biomedical. The primary efficacy endpoint of the Dogwood phase 2 clinical trial is the mean change from baseline in retinal thickness

at 2 months after treatment. Secondary efficacy endpoints include visual acuity improvements at 1 and 2 months after treatment, measured by the mean change in BCVA from baseline. Safety measures are being monitored over the 2-month observation period and include the incidence of adverse events and serious adverse events, including increases in IOP.

Drug administration through the SCS potentially provides a route of access from the anterior region of the eye to treat diseases of the back of the eye like uveitis, retinal vein occlusion, wet age-related macular edema, and diabetic macular edema. In June 2015, the company met with the FDA to review the ongoing clinical activities and discussed the clinical strategy for CLS-TA using SCS drug administration for the treatment of macular edema associated with noninfectious uveitis. An agreement was reached with the FDA for the overall development plan with a single pivotal phase 3 clinical trial, and the company said it is planning to enroll the first patient by December 2015.

Glaukos Announces Settlement of Patent Litigation with Transcend Medical

Glaukos announced that it has entered into a settlement agreement with Transcend Medical to resolve all existing patent litigation between the two companies, according to a company news release.

Under the settlement agreement, Glaukos grants Transcend a covenant not to sue Transcend for patent infringement in connection with Transcend's CyPass Micro-Stent (not FDA approved) devices, appliers, and delivery systems. In exchange, Transcend grants Glaukos a covenant not to challenge the validity or enforceability of any Glaukos patent and will make quarterly payments to Glaukos equal to 1% of future net sales of the CyPass Micro-Stent devices until April 8, 2022, or up to a maximum aggregate payment amount of \$6 million. Glaukos and Transcend have also agreed to file a joint stipulation of dismissal with prejudice of all of their claims against each other in this matter, with each party responsible for its own legal expenses. The settlement agreement eliminates the need for the trial that was scheduled to begin on November 2, 2015, in the US District Court for the District of Delaware.

The covenant not to sue is limited to Transcend's Micro-Stent ab interno devices that facilitate drainage of aqueous humor through the uveoscleral, or unconventional, outflow pathway and are used to treat glaucoma. The settlement agreement does not affect Glaukos' ability to commercialize its iStent Supra Suprachoroidal Micro-Bypass Stent, which accesses the unconventional outflow pathway and is currently being evaluated in a US investigational device exemption pivotal trial. The covenant not to sue expressly excludes devices that drain aqueous humor to other locations such as into Schlemm canal, or aqueous humor collector ducts or channels or implants that elute any drug or another therapeutic agent. ■