Zacks Small-Cap Research

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EyeGate Pharma (EYEG-NASDAQ)

EYEG: Positive EGP-437 Cataract Surgery Data, Clinical Program for Initial CMHA-S Candidate

The detailed assumptions in our Valuation section along with other inputs in our DCF including a 10% discount rate and 2% terminal growth rate, results in a current DCF-generated valuation of approximately $6/share.

Current Price (08/26/16)	$1.75
Valuation	**$6.00**

OUTLOOK

EYEG is a pre-commercial stage company engaged in the development of drugs and drug delivery devices for diseases of the eyes. Their novel iontophoresis drug delivery platform offers a much less burdensome and non-invasive solution to current standard of care for diseases of the eye. Phase 3 pivotal study in anterior uveitis now enrolling – if positive will support NDA filing. Launch could happen by 2018. Out-licensing agreement recently consummated with Valeant/Bausch+Lomb. Clinicals in other indications also enrolling, which could eventually expand the label and respective target market size. Recent Jade acquisition brings complementary, de-risked pipeline. First Jade candidate (EyeGate OBG) could enter clinical program by year-end. Our DCF model, which incorporates indication-specific risk adjustments to account for potential clinical or regulatory failure for each of the three programs, currently values the shares at approximately $6. While representing attractive upside to the current share price, our calculated value should appreciate further on progression through clinical trials of EGP-437 as well as Jade's pipeline.

SUMMARY DATA

52-Week High	**$4.68**
52-Week Low	**$1.59**
One-Year Return (%)	**-52.14**
Beta	**2.25**
Average Daily Volume (sh)	**153,773**
Shares Outstanding (mil)	**9**
Market Capitalization ($mil)	**$16**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**6**
Insider Ownership (%)	**27**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2016 Estimate	**N/A**
P/E using 2017 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**High,**
Type of Stock	**Small-Blend**
Industry	**Med-Drugs**

ZACKS ESTIMATES

Revenue
(in 000s of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2015	0 A	0 A	0 A	0 A	0 A
2016	0 A	235 A	203 E	203 E	641 E
2017					6437 E
2018					7697 E

Earnings per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2015	-$3.23 A	-$0.24 A	-$0.19 A	-$0.35 A	-$2.70 A
2016	-$0.31 A	-$0.46 A	-$0.44 E	-$0.42 E	-$1.64 E
2017					-$0.73 E
2018					-$0.59 E

Zacks Projected EPS Growth Rate - Next 5 Years % **N/A**

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WHAT'S NEW…

Q2 Financial Results, Operating Update…

EyeGate reported financial results for their second quarter ending June 30th and provided a business update. While negligible, EyeGate booked initial revenue. The $235k of revenue in Q2 which relates to government grants which are funding some of Jade's pipeline candidates. Approximately $1.2M remains under the current grants which run through 2017, a portion of which we model as revenue through the remainder of the current year.

Q2 operating expenses of almost $4.1M were up fairly substantially from Q1 ($2.4M) – with almost all of the increase related to a jump in R&D expense, reflecting increased clinical trial costs related to progress of EGP-437 in the phase III study for anterior uveitis as well as the phase 1b/2a study in cataract surgery. EYEG also indicated that they expect the first of Jade's pipeline candidates (JDE-003 now known as "EyeGate OBG") to initiate clinical testing later this year – progress related to which may also be reflected in the higher R&D expense in the quarter. We continue to expect operating expenses to grow sequentially with additional activity in the aforementioned programs including new patients entering the cataract surgery (following recently announced positive topline data) and anticipation of commencement of a randomized, placebo-controlled study next year.

Q2 net income and EPS were ($3.8)M and ($0.46).

Cash: Bolstered by the June 30 sale of 441k common shares (@2.25/share) and 2,777 Preferred A shares ($1k/share, convertible into common @ $2.25/share (i.e. 1.23M common shares) via a registered direct offering which grossed $3.8M (~$3.4M net), cash balance at quarter end was approximately $8M. EYEG believes the current cash balance should be sufficient to fund operations for the next 9 – 12 months.

Cash used in operating activities in the three and six months ending 6/30/16 was $1.4M ($2.3M ex-changes in working capital) and $4.0M ($6.0M ex-changes in working capital) – included in the changes in working capital is $570k and $862k of (cash) license fees received (from Valeant) during the three and six month periods, respectively.

Valeant: Relative to EYEG's commercialization partner for the EGP-437 anterior uveitis indication, to-date EYEG has received a total of $2.52M from Valeant. As a reminder, EYEG initially accounts for the Valeant payments as deferred revenue on the balance sheet – specifics relative to the structure of the milestones, events that trigger payments from Valeant and deliverables which would allow EYEG to recognize this as revenue on the income statement has not been disclosed.

However, additional information contained in the Q2 10-Q, sheds some more light in that regard. This includes that EYEG receives payments when they meet certain objectives towards each milestone as well as when they achieve milestones and they recognize progress payments as revenue when they achieve the related milestone. And while how much of the 'up to $32M.5M that EYEG is eligible to receive in development, regulatory and sales milestones' relates to development and regulatory as opposed to sales, still is an unknown, the 10-Q (language pasted below as an FYI to investors), is helpful in understanding more about the R&D-related milestones..

> *There are four principal R&D milestones under the Valeant Agreement: (i) the Phase 3 Clinical Trial, (ii) the Endothelial Cell Count Safety Trial (a trial to determine that treatment has not adversely affected a patient's corneal endothelial cell density), (iii) the chemistry, manufacturing and control ("CMC") Validation, and (iv) the New Drug Application, or "NDA", filing with the FDA (collectively, the "Four Milestones", and each individually, a "Milestone"). Under the Valeant Agreement, Valeant paid to us an initial upfront payment, and the Company is eligible to receive certain other payments, upon and subject to the achievement of certain specified development and commercial progress of the EGP-437 Product for the treatment of anterior uveitis. The Company received the initial, up-front payment in 2015, which it recorded as Deferred Revenue on its Balance Sheet, and later in 2015 began receiving certain additional payments, based on R&D progress, to continue over several years. We receive payments both when we cross certain thresholds on the way to each Milestone (each, a "Progress Payment"), as well as once we achieve each Milestone. The Company is entitled to retain all of these payments. The Company defers all Progress Payments and capitalize these payments on its Balance Sheet as Deferred Revenue, and recognizes these payments as Revenue once it achieves the Milestone to which the Progress Payment relates. The upfront payment is recognized as Revenue ratably as The Company completes each of the Four Milestones, the amount recognized being the total upfront*

payment times the percentage represented by the proportionate share of fair value of each Milestone relative to the total fair value of the Four Milestones. Accordingly, the Deferred Revenue account on the Balance Sheet is reduced as Revenue is recognized.

On the operational front, the company continues to make progress with its EGP-437 clinical programs as well as with CMHA-S, Jade's cross-linked hyaluronic acid compound.

'EyeGate Ocular Bandage Gel' (OBG) is the new name for JDE-003, the lead CMHA-S candidate which came from the Jade Therapeutics acquisition and which is being developed for corneal repair indications – which could potentially include persistent corneal epithelial defects, following photoreactive keratectomy (i.e. eye surgery) and trauma. As a reminder, the compound has already demonstrated superior efficacy in animal studies to non-crosslinked HA in corneal repair. In early May, EYEG had four posters related to CMHA-S presented at the Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO). EYEG hopes to initiate a clinical pilot study before current year-end.

As we indicated following announcement of the Jade acquisition, we think EyeGate OBG is already de-risked to an extent given the long history of HA being used in human eyes and its broad use and extensive successful testing for corneal repair in animals. A similar cross-linked formulation is already 510(k)-cleared for dermal wound management (BioTime's product), CMHA-S has been vigorously and successfully tested in animals and an identical composition is marketed by BayerDVM (animal health) in the U.S. and Europe under the Remend brand for corneal wound repair which has sold over 600k units. As such, this provides confidence in the potential for positive results of EYEG's upcoming clinical studies.

While EYEG has not provided an update on their expectations in regard to the regulatory pathway, the company previously noted that they believe EyeGate OBG will be able to follow an FDA medical device pathway (as opposed to drug pathway) and were expecting to meet with the agency in Q3 of this year for confirmation. We note that AmbioDisk and Prokera, both amniotic membranes (i.e. disks placed on the eye by clinicians) indicated for use of non-healing epithelial defects also did not follow NDA pathways. Prokera followed 510(k) as a Class II device while AmbioDisk is regulated under Section 361 of the Public Health Service Act by FDA with no clearance required. These are more invasive and require much greater skill to administer than eye drops or a gel (i.e. OBG). This, combined with the strong safety data to-date, may play in EYEG's favor. Assuming they get confirmation of the device pathway, EYEG expects to initiate a clinical pilot study before current year-end.

Relative to EGP-437, while EYEG has not provided an update on the anterior uveitis or macular edema studies in the last couple of months, in early August they did announce encouraging topline data from the phase Ib/IIa post-cataract surgery dose-ranging clinical trial. As a reminder, the study will enroll up to 80 patients (initially enrollment was expected to be 20 patients, which in June increased to 50 and then to 80 in July) which have undergone unilateral cataract extraction and implantation of a monofocal intraocular lens.

Patients are separated into cohorts of 10 patients each; three dosing ranges (4.0 mA-min, 9.0 mA-min and 14.0 mA-min) with the two highest doses at two different treatment schedules (on day 0, day 1 and day 2 or day 0, day 1 and day 4). All three doses have the potential to add another treatment on day 7. Primary endpoint is the proportion of subjects with ACC count of zero on day 14. Secondary efficacy endpoint is the proportion of subjects with a pain score of zero on Day 7.

The top-line data announced a few weeks ago relates to 40 patients (4 cohorts) which were administered iontophoretic EGP-437 at either 9.0 mA-min or 14.0 mA-min on day 0, day 1 and day 2 or day 0, day 1 and day 4, with potential for an additional treatment at day 7 in all cohorts. Results showed patients receiving the 14.0 mA-min dose on days 0, 1 and 4 had the most significant improvement in ACC - with 40% of patients in this group achieving an ACC count of 0 at day 14 (i.e. the primary endpoint) and this increased to 88% on day 28.

In addition all patients receiving the iontophoretic treatment reported reduced pain at all time points with 90% having no pain as early as day 1 and increasing to 100% on day 14. In addition there was no steroid-related increase in intraocular pressure reported.

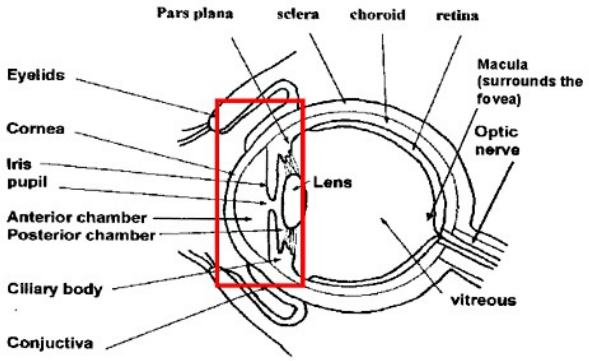
EYEG expects to enroll three additional cohorts at other doses and dosing regimens with the expectation of further improving on the efficacy data to-date. They hope to have top-line data from these additional cohorts in Q4 of this year and, assuming positive results, expects to initiate a randomized, placebo-controlled clinical trial of EGP-437 in cataract surgery patients by year-end.

BACKGROUND

Non-Infectious Anterior Uveitis

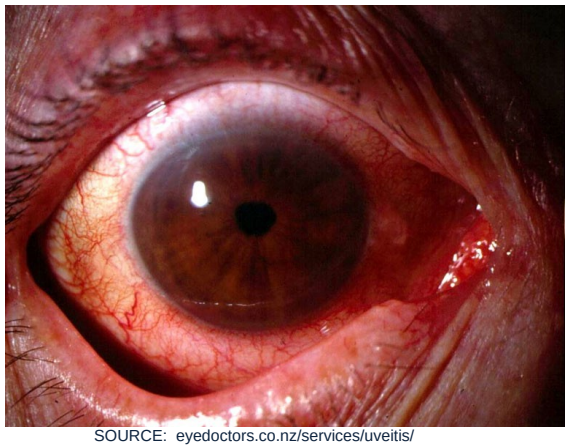
Uveitis is a generic term used to describe inflammation of the uvea. It can occur either in isolation or be the result of an underlying medical condition in other parts of the body. The uvea is the middle layer of the eye, below the white of the eye, and consists of the iris (colored portion), choroid layer (connective tissue) and ciliary body (secretes liquid). Infectious uveitis is caused by a virus or bacteria in the eye while non-infectious uveitis is endogenous, or the result of a disease elsewhere in the body.

Non-Infectious Anterior Uveitis



Eye Structures Involved in "Anterior Uveitis"

SOURCE: uveitis.net



SOURCE: eyedoctors.co.nz/services/uveitis/

Symptoms include redness, inflammation and pain in the eye, photophobia (extreme sensitivity to light), blurred vision and change in shape or size of the pupil. If left untreated, anterior uveitis can result in development of other complications including glaucoma, formation of synechiae, cataracts, macular edema, retinal detachment and, eventually, even blindness.

Prevalence of uveitis in the U.S. is roughly (estimates vary depending on source) 50 people per 100k population, or approximately 165k. U.S. incidence estimates also vary by study – the most cited study estimates range from a low of about 17 to a high of about 52 people per 100k population[1,2,3,4] - an average of ~35 per 100k, or approximately 115k incidents per year. Non-infectious uveitis, which is the initial indication that EYEG is pursuing, is the most common form of uveitis, accounting for about 75% of all cases and about 90% of these are located at the anterior of the eye (i.e. non-infectious anterior uveitis).

Estimated U.S. Incidence and Prevalence

	Uveitis	Non-Infectious	Non-Infectious Anterior
Incidence	115,000	86,250	77,625
Prevalance	165,000	123,750	111,375

[1] Acharya NR, Tham VM, Esterberg E, et al. Incidence and Prevalence of Uveitis: Results From the Pacific Ocular Inflammation Study. JAMA Ophthalmol. 2013;131(11):1405-1412. doi:10.1001/jamaophthalmol.2013.4237

[2] Darrell RW, Wagener HP, Kurland LT. Epidemiology of uveitis: incidence and prevalence in a small urban community. Arch Ophthalmol. 1962;68:502-514

[3] Gritz DC, Wong IG. Incidence and prevalence of uveitis in Northern California: the Northern California Epidemiology of Uveitis Study. Ophthalmology. 2004;111(3):491-500, discussion 500

[4] Suhler EB, Lloyd MJ, Choi D, Rosenbaum JT, Austin DF. Incidence and prevalence of uveitis in Veterans Affairs Medical Centers of the Pacific Northwest. Am J Ophthalmol.

Uveitis treatment involves arduous dosing regimen…

Dexamethasone phosphate is a corticosteroid, administered either orally in pill form or as an injection, which has anti-inflammatory and immune-response modifying effects. It is used for rheumatic diseases as well as other conditions such as allergies, intestinal disorders, eye diseases and other ailments. Topical corticosteroids are considered the first line of treatment for uveitis with dexamethasone and prednisolone acetate being the most widely used. Corticosteroids are used to reduce inflammation which is caused by the build-up of white blood cells in the anterior chamber (see diagram above) of the eye. The primary endpoints of EYEG's clinical trials evaluating EGP-437 and EyeGate Delivery System for the treatment of anterior uveitis are reduction of anterior chamber white blood cell count.

Diagnosis and evaluation, which includes patient history and ocular examination, are done to rule out other possible causes and to determine severity of the disease. Anterior uveitis is classified as either mild, moderate or severe which determines the initial dosing regimen as well as frequency of follow up visits to an ophthalmologist. The follow-up schedule and prednisolone acetate dosing regimen in the table below are adapted from the reference guide, *Primary Care of the Anterior Segment*, by Louis Catania.[5]

Anterior Uveitis Dosing and Follow-Up Schedules

	Severity		
	Mild	Moderate	Severe
Frequency of follow-up visits	Every 4 to 7 days	Every 2 to 4 days	Every 1 to 2 days
Recommended dosing	Two to four times per day	Four times per day	Every 2 to 4 hours

The above table lists the recommended initial dosing. The total regimen can last four to six weeks and include 150 or more drops. Regular follow-up visits are necessary to ascertain response and determine if and when to begin tapering dosage as **regular use of corticosteroids is associated with certain adverse side effects including immune suppression, accelerating cataract formation and increased ocular pressure**. Eye drops are an inherently inefficient route of administration and, depending on how much of the drop gets in the eye (versus runs down the face) and penetrates protective tissue (eyes are adept at keeping out foreign substances), the amount of active ingredient that reaches its intended target can vary widely. This is another reason as to why drops must be dosed so frequently and regular check-ups are so important.

***Iontophoresis** is defined as the transfer of ions. It is the use of a weak electrical current to deliver drugs through or across tissue and other biologic substances. An ionic therapeutic substance is placed under an electrode of like-charge (i.e. ion and electrode are both of either positive or negative polarity). The like-charges create electropropulsion as two substances of similar charge repel, pushing the therapeutic substance into the tissue.*

The burdensome dosing schedule results in patient compliance issues. When patients fail to complete the recommended dosing regimen, the risk of treatment failure increases. In fact, lack of compliance is the most common cause of treatment failure. As noted above, significant complications can result if uveitis is not effectively treated.

EYEG's Treatment Solution: EyeGate II Delivery System and EGP-437

The EyeGate II Delivery System delivers a precise dose of EGP-437, a proprietary and reformulated version of (generic) dexamethasone phosphate, to the eye through the use of iontophoresis. The procedure is relatively fast, is non-invasive and is efficient in delivering drugs to their intended target within the ocular tissue. It has been used in over 1,700 treatments to-date.

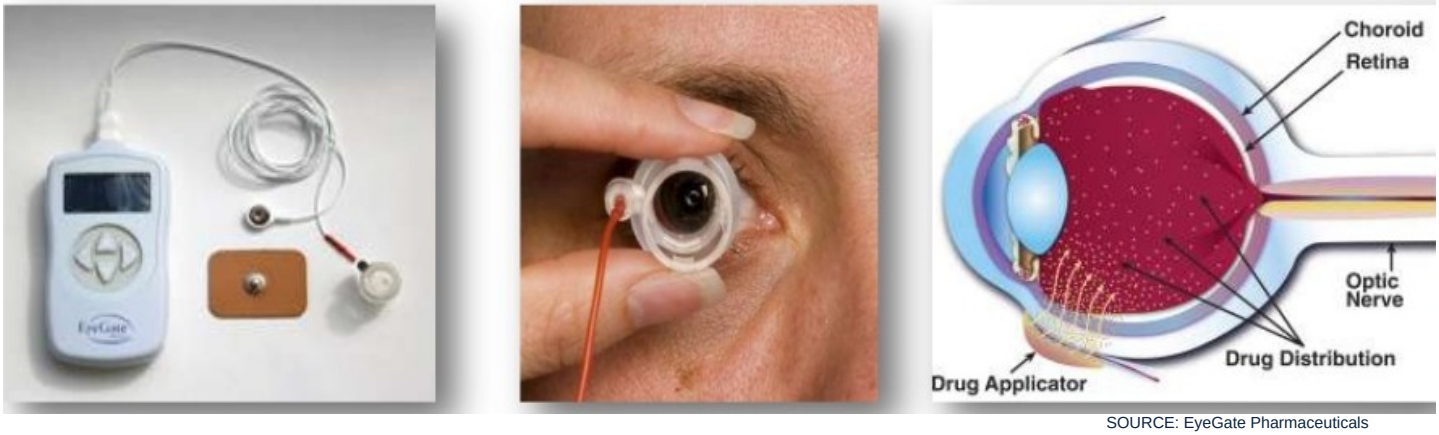
As opposed to the rigorous dosing schedule of eye drops for conditions such as anterior uveitis, treatment with EYEG's combination product can be completed in only one to four minutes over just two or three visits to an eye doctor. It has also been shown to effectively deliver drugs to the posterior of the eye, offering a non-invasive approach to traditional eyeball needle injections for treatment of conditions such as macular edema. As such, EyeGate believes their combination therapy provides a solution to the patient burden, non-compliance and invasiveness issues associated with conventional therapy.

[5] Catania, L. J. (1995). Primary care of the anterior segment. Norwalk, CT: Appleton & Lange

EyeGate II Delivery System consists of a small handheld generator, a return electrode and an ocular applicator. The generator produces and delivers the iontophoresis-inducing current. It is easily programmed through an LED screen for the correct dosage and current. The screen displays delivery of the current in real-time, the amount of the drug delivered and the treatment time remaining. The generator is the only portion of the delivery system and drug that is not a single-use disposable.

The return electrode, which is placed on the patient's forehead, is used to create a continuous current. The ocular applicator is filled with EGP-437, topical anesthesia is applied to the surface of the eye and the applicator is then placed over the sclera of the eye. A soft foam pad on the applicator makes contact with the eye – EYEG's instructional video (https://youtu.be/v7oSLe-bLWo) on their website notes that the applicator is as comfortable as a contact lens. Drug delivery commences when the generator is turned on, delivering a low electrical current to an electrode within the applicator and initiating iontophoresis.

The electrode electrolyzes water molecules within the applicator, converting them into either hydronium or hydroxide molecules, depending on whether positive (cathodic) or negative (anodic) polarity is used. Electropropulsion, created by the like-charged ions and molecules, pushes the drug molecules into the tissues of the eye until they reach their intended target. The drug delivery takes about one to four minutes, after which the applicator is removed and the procedure is completed. Dose can be changed by adjusting the current and application time.



SOURCE: EyeGate Pharmaceuticals

Issues of Traditional Ophthalmic Drug Delivery Address by Eyegate's System

Anterior Eye Conditions	Posterior Eye Conditions
• Rigorous dosing regimen	• Needle-in-the eye patient anxiety
• Biological barriers in eye inhibit drug penetration	• Several injections over multiple weeks required
• Patient non-compliance	• Risk of inflammation and infection
• Side effects; IOP, cataracts and others	• Requires experienced clinician & companion
	• Complications such as IOP, retinal detachment

Clinical Data in Non-Infectious Anterior Uveitis: EYEG has completed two non-infectious anterior uveitis clinical studies. The first, which completed in 2009, was a phase I/II dose-ranging study which demonstrated

the combination product produced inflammation lowering effects with no corticosteroid mediated effects and found the most effective dose to be the lowest one tested. The second study, a phase III trial which used the dose found to be most effective in the prior dose-ranging study, just missed the primary efficacy endpoint of non-inferiority to standard of care. However, FDA recently communicated to EYEG that if a planned new phase III study demonstrates non-inferiority, that that data, along with results of the completed phase III study, will be sufficient to support a New Drug Application (NDA) filing.

- ***Phase I/II dose-ranging study: lowest dose deemed most effective…***

EYEG's first non-infectious anterior uveitis clinical trial was a phase I/II, single-arm dose-ranging study (clinicaltrials.gov ID:NCT00694135) to determine a safe and effective dose of EGP-437. Non-infectious anterior uveitis was defined as having anterior chamber cell (ACC) scores of ≥1.5 (on a scale of 0 – 4, lowest – highest), which corresponds to a cell count of ≥11. Enrollment of the multi-site, double-blind study consisted of 40 patients (40 eyes), all of which received treatment with EGP-437 delivered by iontophoresis via the EyeGate II Delivery System. Patients were randomized to receive one of four EGP-437 doses (dexamethasone phosphate ophthalmic solution 40mg/mL) with 10 patients in each arm; 1.6 mA-min @ 0.4 mA[6], 4.8 mA-min @ 1.2 mA, 10 mA @ 2.5 mA and 14 mA @ 3.5 mA. Each dose was administered only once and for approximately four minutes. Treatment was administered on Day 0, follow-up exams were conducted on Days 1, 7, 14 and 28.

Results (table below): 19 of the 40 patients (48%) and 24 of the 40 patients (60%) achieved an ACC score of zero within 14 days and 28 days, respectively. Interestingly, the greatest proportion of patients achieving both ACC scores and ACC cell counts of zero at both the 14 day and 28 day follow-up were in the lowest dose (i.e. 1.6 mA) cohort. The lowest dose group also had the highest proportion of patients (80% vs. 60% of the other three groups) which experienced an ACC score reduction of 0.5 or more at Day 28. The mean change in ACC score from baseline to Day 28 ranged from a maximum of -2.25 in the 1.6 mA dose group to a minimum of -2.00 in the 14.0 mA dose group. The 1.6mA dose was chosen as the most effective dose. Achievement of an ACC score of zero by Day 14 was considered statistically significant (p=0.032) at a 95% CI. Treatment was well tolerated with no corticosteroid mediated effects.

		Treatment Group				
Characteristic	Statistic or Category	1.6 mA-min (N = 10)	4.8 mA-min (N = 10)	10.0 mA-min (N = 10)	14.0 mA-min (N = 10)	Total (N = 40)
ACC **Score** of Zero	Day 14	8 (80%)	6 (60%)	2 (20%)	3 (30%)	19 (48%)
	Day 28	8 (80%)	6 (60%)	5 (50%)	5 (50%)	24 (60%)
ACC **Count** of Zero	Day 14	4 (40%)	1 (10%)	1 (10%)	1 (10%)	7 (18%)
	Day 28	6 (60%)	2 (20%)	1 (10%)	5 (50%)	14 (35%)

SOURCE: EyeGate YE 2015 10-K

- ***Initial Phase III Study; Similar Clinical Response as PA Although Endpoint (Barely) Missed…***

The phase III randomized, double-blind, placebo-controlled study (clinicaltrials.gov ID:NCT01505088) that followed the dose-ranging trial was powered as non-inferiority to standard of care. The study was conducted at 45 U.S. sites and included 193 patients with non-infectious anterior uveitis (ACC count ≥ 11) which were randomized to treatment, consisting of EyeGate combination treatment of 4.0 mA-min @ 1.5mA on Day 0 and Day 7 (in addition to placebo drops for 28 days), or control, consisting of prednisolone acetate 1% eyedrops for 28 days (in addition to sham EyeGate treatment (sodium buffer solution) on Day 0 and Day 7).

While dexamethasone is one of the most potent of all corticosteroids and has anti-inflammatory effects that are as much as 10x greater than that of prednisolone, it does not penetrate the anterior chamber of the eye nearly as well as prednisolone. This is the reason that prednisolone is considered standard of care for anterior uveitis and why it was used as the control in these clinical studies. And while absorption of dexamethasone dosed as drops is inhibited by corneal and conjunctival barriers, these challenges are at least partially overcome with the use of iontophoresis which propels the drug into the tissue. And the drug's accommodating chemical profile make it highly water soluble which also adds to its attractiveness with iontophoresis delivery.

[6] mA is abbreviation for milliampere (one thousandth of an ampere)

Per pre-study communications with FDA, prednisolone acetate (PA) administered at least 4x per day was the recommended standard of care (i.e. control). However, EYEG chose to use a more aggressive control regimen, administering PA 8x per day in week one, 6x per day in week two and 4x per day in weeks three and four (for a total of 154 drops over 28 days).

Primary endpoint was proportion of patients with ACC count of zero at Day 14 (i.e. complete response). Several **secondary** efficacy outcomes were also measured including proportion of patients with ACC counts at Days 7, 28 and 56, mean change from baseline in ACC count and score at Days 7, 14, 28 and 56 and proportion of patients with ACC count and score reduction from baseline of one or more units at Days 7, 14, 28 and 56, and time to anterior chamber cell count and score of zero.

Results were presented on two separate patient populations; intent to treat (ITT) and per protocol (PP). ITT is generally used in clinical trials to account for non-compliance of trial design, protocol deviations drop-outs or anything after randomization. ITT results are generally considered conservative to treatment effect. PP is typically considered the population that remained in the study through the measurement endpoints and did not violate any of the trial protocol

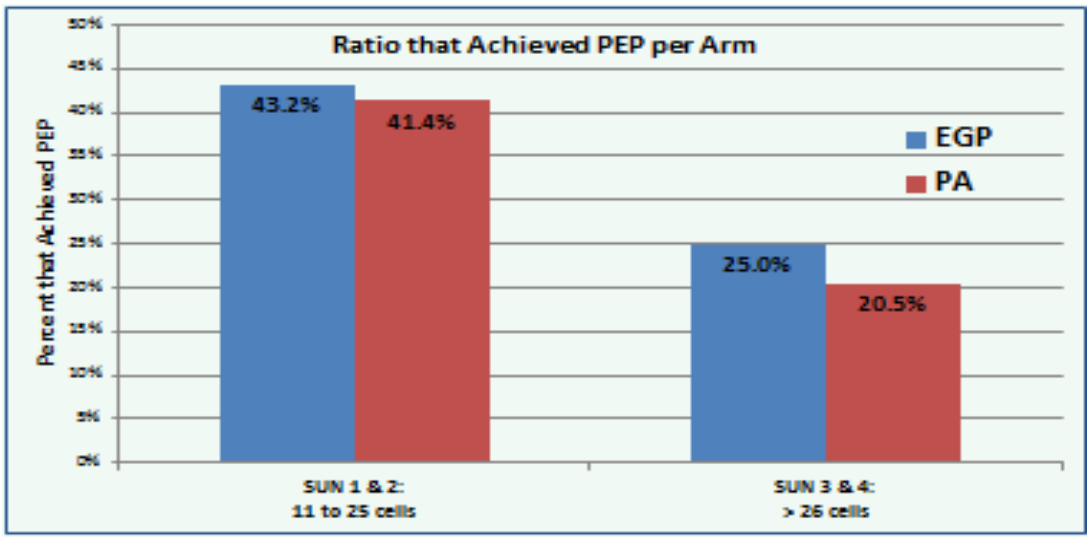
- **ITT**: defined as all randomized patients (193) who were treated with at least one dose of study medication, have a valid baseline efficacy and at least one valid post-randomization efficacy measurement and all data associated with these subjects, until the visit following initiation of any rescue therapy.
- **PP**: 169 patients met the PP population parameters which included those that had a Day 14 ACC count and without any significant protocol deviations. Of the ITT population, 24 patients had protocol violations prior to Day 14 including;
    - 14 in EyeGate treatment arm, 10 of which either needed to be rescued and/or did not receive the second (of two) iontophoresis treatments, 1 which needed non-ocular surgery, 2 which were unable to continue with follow-up visits and 1 which withdrew consent
    - 10 in the PA arm, 8 of which either needed to be rescued and/or did not receive the full amount of PA and 2 which had their Day 14 visit twelve and thirty days later than that visit timeframe

Results: (per information contained in company public filings) While response rates were similar in both the ITT and PP populations, non-inferiority (as pre-defined in the study protocol) was just missed.

- IIT: EGP-437 treatment arm had 32 (out of 96) patients with complete response (i.e. ACC count of zero at Day 14) while PA arm had 32 (of 97) with complete response. There was no difference in response rates between the two arms at a 95% C.I., however, the non-inferiority margin, at -12.94%, just missed statistical significance of the pre-determined non-inferiority margin of -10%
- PP: EGP-437 treatment arm had 31 (of 82) patients, or 37.8%, with complete response while PA arm had 31 (of 87), or 35.6%, with complete response. Again, while there was no difference in response rates, the non-inferiority margin (-12.37%) just missed the pre-determined non-inferiority margin (-10%) at a 95% C.I.

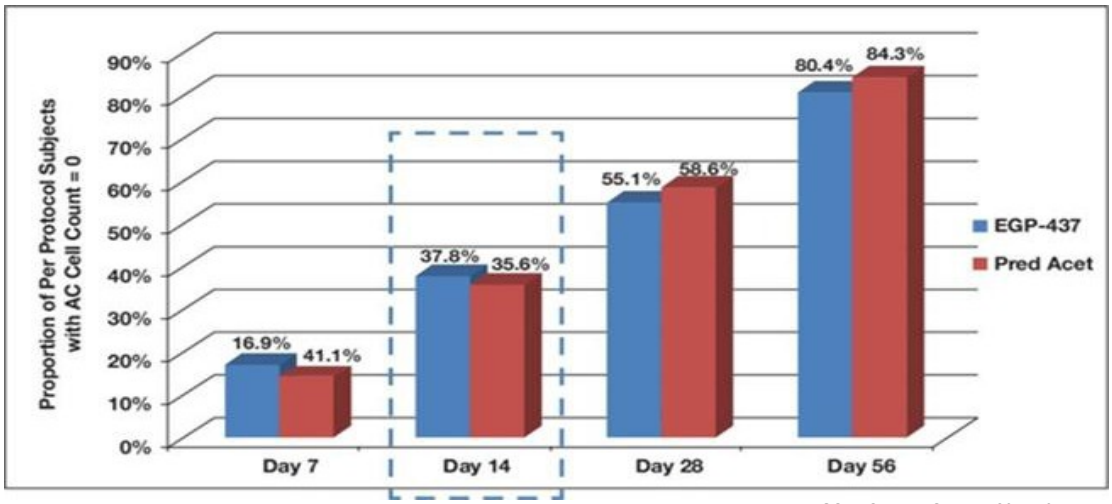
Additional Observations: Along with no difference in response rates between both arms on the primary endpoint, secondary measures and other observations also support the efficacy of EGP-437 combination therapy;

- Greater Proportion of High ACC Count Patients in EGP-437 Arm: a higher proportion of EGP-437 patients (52 of 96, or 54%) had baseline ACC counts greater than 25 as compared to those in the PA arm (40 of 97, or 41%). A post-hoc analysis was done on these high ACC count (i.e. potentially harder to treat) patients with better efficacy favoring the EGP-437 arm. Among the patients with baseline ACC of 11 to 25 cells, 43.2% of EGP-437 patients met the primary endpoint (i.e. ACC count of zero at Day 14) while only 41.4% of PA patients did. Among the patients with baseline ACC > 26 (i.e. – more severe cases), 25% of EGP-437 patients met the primary endpoint while only 20.5% of PA patients did (chart below).



SOURCE: EyeGate

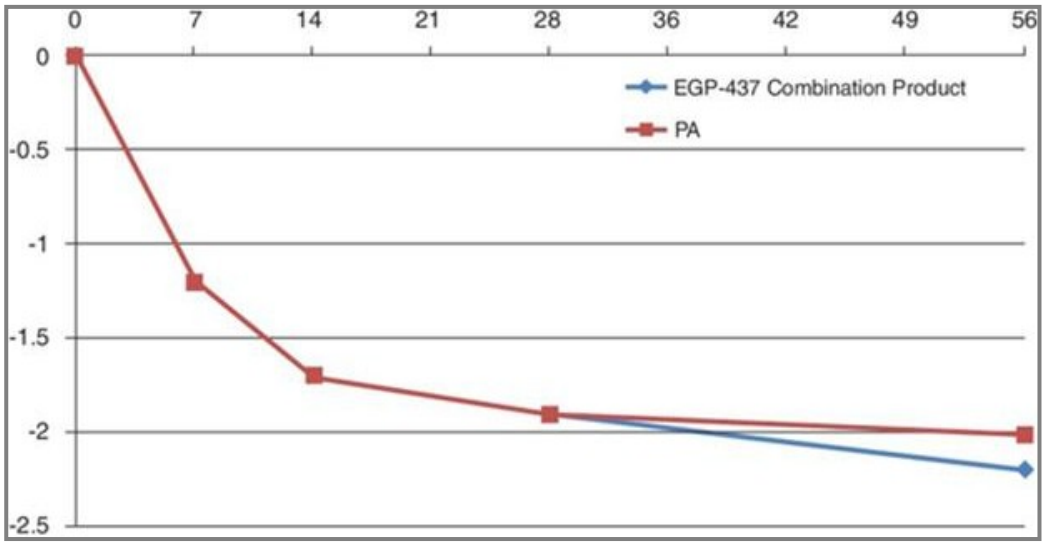
- Similar Complete Response Timeframes: "Time to anterior chamber cell count and score of zero" was a secondary endpoint. Despite the baseline difference in severity of disease (as measured by ACC count), the time to reach ACC count of zero was generally similar in both arms throughout the study (chart below). However, at Day 7, after just one iontophoresis treatment, the EGP-437 arm showed a statically significant superior response with 16.9% of patients achieving complete response, compared to just 14.1% of PA patients. This non-inferiority margin was -7.82%, within the pre-determined margin of -10% at 95% C.I.



SOURCE: EyeGate YE 2015 10-K

- Similar Reduction in ACC Count of One or More Units: "Proportion of subjects with ACC count and score reduction from baseline of one or more units" was another secondary endpoint. On this measure the two arms were similar, although the non-inferiority margin (-13.97%) was just outside the non-inferiority margin at 95% C.I.

- Similar Change from Baseline ACC Score: "Mean change from baseline in ACC count and score" at Days 7, 14, 28 and 56 was another secondary endpoint. This was similar between both arms throughout the study (chart below) with an incremental benefit to the EGP-437 treatment group at Day 56



SOURCE: EyeGate YE 2015 10-K

- Safety: Lower Incidence of IOP in EGP-437 Arm: corticosteroid use is associate with an increase in intraocular pressure (IOC), which can eventually result in permanent damage to the eye. IOC measurements were taken at Days 7, 14, 28 and 56 and compared to baseline.
    - There were 2.4x more incidents of increase in IOP in the PA arm as compared to the EGP-437 arm. 17 incidents of an increase in IOP among 14 patients (of 96, or ~15%) were recorded in the EGP-437, compared to 41 incidents among 24 subjects (of 97, or ~25%) in the PA arm
    - No patients in the EGP-437 therapy arm experienced any significant increase (i.e. over 20mmHg) in IOP while one subject in the PA arm reported an IOP increase of 27mmHg. In terms of IOP-related adverse events, one patient in the EGP-437 arm reported an adverse event (~3 weeks following rescue) and six patients in the PA arm reported IOP-related adverse events. NOTE: EYEG's 10-K, where we sourced this trial data and information, did not provides specifics of the nature or severity of the adverse events, only that they were related to IOP

Key Takeaways:

- While the primary endpoint was (barely) missed, EGP-437 combination therapy appeared to be similarly effective as standard of care (i.e. PA)
- There was a trend in the data favoring EGP-437 combination therapy in patients with higher ACC counts (i.e. generally considered more difficult to treat)
- EGP-437 combination therapy consisted of two treatments at Days 0 and 7 with administration taking ~5 minutes each session. This compares to PA therapy which consisted of 4 – 8 eye drops every day over the course of four weeks, aggregating to a total of 154 drops. While the PA regimen was perhaps more aggressive than that recommended by FDA (of "at least four drops per day"), this highlights how much more burdensome conventional therapy is
- Safety was at least comparable, or perhaps favoring EGP-437 combination therapy particularly in lower IOP

❖ ***New, Pivotal Phase III Study..***

In May 2015 EYEG announced that FDA communicated that if a planned new phase III study demonstrates non-inferiority, that that data, along with results of the earlier phase III study (discussed above), will be sufficient to support a New Drug Application (NDA) filing.

This non-infectious anterior uveitis "confirmatory study" is randomized, double-blind, placebo-controlled and designed to demonstrate non-inferiority of EGP-437 combination therapy to PA 1%. Up to 250 patients (~125 each arm) with anterior segment uveitis (ACC count $\geq$ 11) are expected to enroll at approximately 60 U.S. sites. Primary efficacy endpoint is the same as the initial phase III study (i.e. ACC count of zero at Day 14).

Patients will be randomized to either three treatments of EGP-437 combination therapy (Days 0, 4 and 9) plus placebo eye drops or PA 1% plus sham EGP-437 combination therapy. The design of this confirmatory study, while similar to the initial phase III anterior uveitis trial, has some important differences which should improve the chances

of meeting the primary efficacy endpoint. This includes its larger size (greater chance of fleshing out statistical significance), three EGP-437 combination treatments (1.5 mA-min @ 2.7mA) instead of two (4.0 mA-min @ 1.5mA) and randomization based on severity of the disease (to eliminate the potential bias of more severe patients which was seen in the AGP-437 arm in the initial study).

	First Phase 3	Confirmatory Trial
Number of Subjects	193	250
Number of Treatments	2 (Day 0 and Day 7)	3 (Day 0, Day 4 and Day 9)
Randomization	1:1	1:1 and SUN scale severity
Primary Endpoint	ACC Count= 0 at Day 14	

SOURCE: EyeGate

Timelines: The first patient was enrolled in the confirmatory study in January 2016. Per EYEG's most recent public communications regarding timelines, they expect the study to be fully enrolled by current year-end and to have top-line data in Q1 2017. Those timelines may be do-able depending on the rate of enrollment. For comparison, per clinicaltrials.gov, the initial phase III study started in December 2011 and had a primary completion date (final data collection date for primary outcome measure) of February 2013 – or ~14 – 15 months. This ~14 months included 12 months of enrollment and 2-month follow-up period. While the confirmatory study will enroll ~23% more patients, the pace of enrollment should benefit from presumed use of some of the same clinical sites and investigators.

U.S. Regulatory Pathway: Assuming positive results (i.e. primary efficacy endpoint met and acceptable safety profile), EYEG expects to file for U.S. regulatory approval/clearance of both the EyeGate II Delivery system and EGP-437 simultaneously. EyeGate has already received confirmation from FDA that their delivery system is considered a Class II device but can pursue clearance through the (relatively simple) 510(k) clearance pathway. For EGP-437, which must be approved through a New Drug Application (NDA), EyeGate intends to file a 505(b)(2) NDA.

Relative to the device. EYEG's 510(k) will cite two existing iontophoresis devices which deliver drugs through the skin, one of which is DJO Global's (Empi's) Dupel II Buffered iontophoresis electrode for use of delivery of lidocaine and epinephrine. FDA has agreed that these are acceptable to use as predicates.

The 505(b)(2) NDA relates to, "an application that contains full reports of investigations of safety and effectiveness but where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference." It "permits FDA to rely, for approval of an NDA, on data not developed by the applicant."[7] FDA allows 505(b)(2) applications in circumstances where there are changes to an approved drug such as, formulation, dosage form, strength and route of administration, among others. EYEG has referenced Decadron, a topical dexamethasone formulation, which they believe they may be able to use the existing safety and efficacy literature of for filing of EGP-437 under the 505(b)(2) pathway.

Based on our communication with EyeGate, management is comfortable, based on their interaction and communication with FDA including the agency accepting a preclinical and clinical data protocol based on the 505(b)(2) NDA route, that this is an acceptable pathway. And importantly, EGP-437 has demonstrated what appears to be an acceptable safety profile in the five clinical studies in which it has been used. The initial phase I/II non-infectious anterior uveitis trial was conducted under the initial IND, submitted to FDA in April 2008. The IND was then subsequently amended for additional studies.

Follow-On Indications: Macular Edema and Cataract Surgery

While EYEG expects to enter the market with a non-infectious anterior uveitis indication, they have had their sights on a broader label and one that includes more prevalent ophthalmic diseases (i.e. larger market sizes) and harder to treat (i.e. potential for rapid market penetration) back-of-the-eye conditions. Macular edema, which is a swelling of the macula (center portion of the retina) due to a build-up of fluid leaking from blood vessels, is traditionally treated with drug injections, laser therapy or intravitreal implants. EYEG has initiated a phase Ib/IIa study in

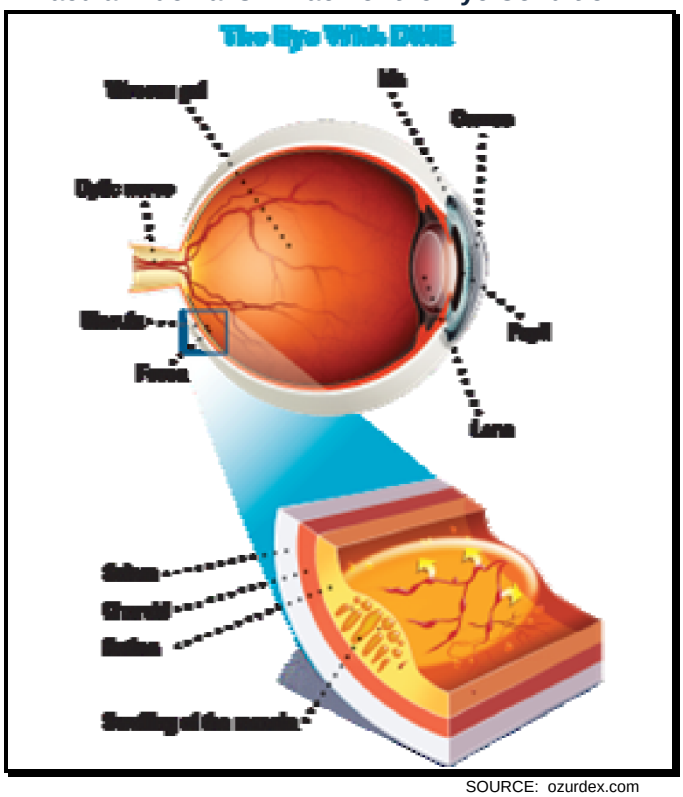
[7] Guidance for Industry. Applications Covered by Section 505(b)(2). US Dept of HHS/FDA/CDER. Oct 1999

macular edema. Cataract, the leading cause of blindness, results in over 3 million cataract surgeries per year in the U.S. and may represent an attractive market for EyeGate's combination therapy.

- **Macular Edema:** ***EGP-437 can treat back of the eye, initial clinical data is positive…***
  Formation of macular edema can be the result of a variety of conditions and circumstances. While it is most commonly associated with type 2 diabetes, age-related macular degeneration can be a direct cause. Chronic uveitis or blockage of a vein (retinal vein occlusion) can also be contributors as can complications following cataract surgery such as cystoid macular edema (cyst-like fluid build-up in macula).

  Diabetic macular edema affects up to 7% of people with diabetes[8], or ~2M Americans. Estimated incidence of cystoid macular edema varies widely depending on the source, examination technique and definition of the condition but is believed to be ~1% - 14% of cataract surgery patients, or ~30k – 400K Americans. Standard of care of macular edema includes NSAID and cortisone drops, laser retinal photocoagulation, intravitreal injections (corticosteroids and anti-VEGF drugs) and intravitreal implants. These all have drawbacks; NSAID's can cause burning, stinging and even "corneal melting", laser retinal photocoagulation often damages nerve cells in the retina causing some vision loss, drops not only must be dosed continuously but they are highly inefficient in reaching the back of the eye and can have adverse side effect, injections are highly invasive, cause patient skittishness, risk infection and eye damage and require a trained ophthalmologist to administer, intravitreal implants can migrate within the eye which can cause permanent eye damage.

Macular Edema Is A Back-of-the-Eye Condition



SOURCE: ozurdex.com

EYEG's phase Ib/IIa multi-site, open label proof-of-concept clinical study (clinicaltrials.gov ID: NCT02485249) **of EGP-437 therapy in patients with macular edema** associated with retinal vein occlusion (RVE), diabetic macular edema (DME) or post-surgical (cystoid) macular edema (CME) is ongoing. Subjects received three treatments of EGP-437 iontophoresis therapy at 14mA-min (3.5mA) on days 0, 4 and 9. Primary outcome was reduction in mean central subfield thickness on day 4, day, 9 and day 14. Ozurdex, a dexamethasone intravitreal implant marketed by Allergan (NYSE: AGN) and indicated for treatment of macular edema, retinal vein occlusion and non-infectious posterior uveitis, was administered as control to patients that did not respond to EGP-437 combination therapy at day 14 and were re-evaluated at day 28.

[8] Curr Diab Rep. 2012 Aug;12(4):346-54. doi: 10.1007/s11892-012-0283-6. *Current epidemiology of diabetic retinopathy and diabetic macular edema.* Ding J1, Wong TY.

In November 2015 EYEG announced results of the first-leg of the study, which included 19 patients (results on 18). Nine patients with pseudophakic eyes (i.e. those with implanted intraocular lens) were enrolled with the following conditions; six with DME, three with RVO. Nine patients with phakic eyes (i.e. those with natural lens) were enrolled with the following conditions; four with DME, three with RVO and two with CME. **Safety profile was considered excellent** with no increase in IOP – which is particularly noteworthy given that the dose in this study was three times that of the dose in the initial phase III anterior uveitis study.

There was a clear efficacy signal, demonstrating that EGP-437 combination therapy can deliver drugs to the back of the eye. The study also showed that pseudophakic eyes responded better than phakic eyes. Nine patients with pseudophakic eyes and nine phakic eyes were in the study.

- While **phakic eyes** responded relatively poorly, with just an 8% mean thickness reduction observed in only 2 of 9 patients and minimal or no response in the remaining seven, pseudophakic eyes showed a relatively strong response.
- Seven of nine **pseudophakic eye** patients had a positive response including three with greater than 25% reduction in edema at day 14, one of which showed a 67% reduction. Just three patients were given Ozurdex and only two of which showed minimal or no response to EGP-437 therapy.

Edema (μ)	V1 Day 0	V2 Day 4	V3 Day 9	V4 Day 14
Phakic	451	461 (-1.6%)	455 (-0.2%)	470 (-3.6%)
Pseudophakic	540	448 (17%)	416 (23%)	427 (21%)

7 of 9 Pseudophakic Showed Positive Response Incl. 3 >25% and 1 = 67%

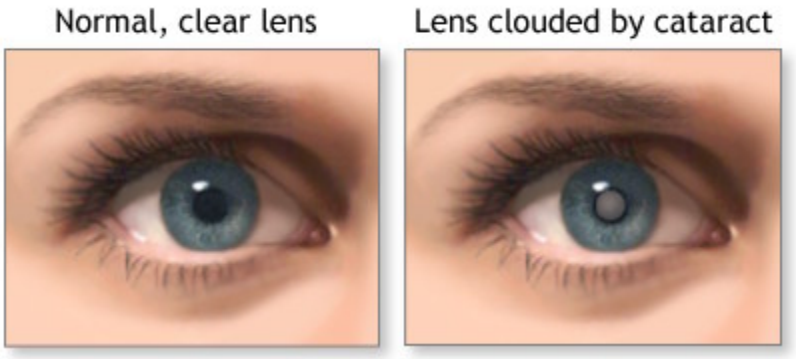
Patient Information				OCT Measurements				IOP			
	ME DX	Gender	DOB	Visit 1 Day 0	Visit 2 Day 4	Visit 3 Day 9	Visit 4 Day 14	Visit 1	Visit 2	Visit 3	Visit 4
PSEUDOPHAKIC SUBJECTS											
1	DME	Male	21-Dec-58	694	615	614	616	12	15	15	14
					11.4%	11.5%	11.2%				
2	CME	Female	23-May-54	623	569	512	566	14	15	12	10
					8.7%	17.8%	9.1%				
3	BRVO	Female	25-Dec-50	558	531	522	503	14	13	15	18
					4.8%	6.5%	9.9%				
4	pCME	Female	6-Dec-48	500	325	304	298	10	10	12	10
					35.0%	39.2%	40.4%				
5	DME	Male	21-Sep-52	758	392	249	273	16	14	13	17
					48.3%	67.2%	64.0%				
6	BRVO	Male	20-Sep-51	318	317	294	291	11	11	11	11
					0.3%	7.5%	8.5%				
7	DME	Female	2-Nov-53	521	496	515	523	18	18	20	20
					4.8%	1.2%	-0.4%				
8	BRVO	Female	24-Dec-26	502	413	358	368	12	14	13	16
					17.7%	28.7%	26.7%				
9	DME	Female	13-Feb-44	390	372	380	408	13	14	14	12
					4.6%	2.6%	-4.6%				
Mean				**540**	**448**	**416**	**427**	**15**	**14**	**14**	**14**
					17.1%	22.9%	20.9%				

The **second leg** will enroll an additional 15 patients; 5 with phakic eyes and 10 with pseudophakic eyes. Five (three with phakic, two with pseudophakic) of the patients in the first trial which had minimal or no response to EGP-437 therapy but did respond well to Ozurdex will continue in the second leg. As it was observed that edema comes back when the drug clears the tissues, this extension study will use a modified dosing regimen; three consecutive days of EGP-437 iontophoresis treatments at the same dose. And as data from the first leg demonstrated some patients with pseudophakic eyes responded better than those with phakic eyes, this second leg will also evaluate the efficacy of EGP-437 combination therapy in phakic versus pseudophakic eyes to collect additional data on the differences in the responses of both groups. Interim data had previously been expected to be available in 1H 2016, although this timeline has slipped – we hope to hear an update in the near-term. Data from this study, assuming positive, will then be used to design a larger, later-stage clinical trial.

Our comments: Macular edema represents a potentially receptive and large market for EYEG given the seriousness and high incidence of the disease as well as the lack of conventional, effective non-invasive methods to treat it. EYEG's early stage studies have shown the ability to deliver EGP-437 to the back of the eye to treat conditions such as macular edema. As back-of-the eye conditions are more difficult to treat than, for example anterior uveitis, if effectiveness of EGP-437 combination treatment in macular edema is confirmed in larger studies, we think this indication could offer significant opportunity for EYEG.

- **Post Cataract Surgery:** ***EGP-437 can treat back of the eye, initial clinical data is positive…***

Cataract, or a clouding of lens, is most commonly the result of ageing and is the leading cause of blindness across the globe. Approximately 21 million people in the U.S. over the age of 40 have cataract in at least one eye, ~6 million of which have undergone surgery to have their lens removed. About 3.6 million cataract surgeries are performed in the U.S. each year and about 20 million worldwide.



SOURCE: A.D.A.M. / umm.edu

Standard of care to manage post-operative cataract surgery inflammation are NSAIDs and corticosteroids. EYEG conducted a phase II study (clinicaltrials.gov ID: NCT01602068) with EGP-437 combination treatment in cataract surgery which completed in 2013. They decided to apply EGP-437 treatment prior to (4.0 mA-min at 1.5 mA one day prior to surgery) surgery in order to avoid putting the delivery device directly on a post-surgery open wound. Primary endpoint was proportion of subjects with ACC count of zero on day 7. While we were unable to find the detailed results in the public domain, EYEG has noted that "the surgical procedure eliminates or washes out any remaining drug product from the ocular tissue that becomes inflamed post-surgery" - presumably indicating that the study failed to meet the efficacy endpoint.

EYEG has revised the trial design and initiated another cataract surgery study. The study will enroll up to 80 patients (initially enrollment was expected to be 20 patients, which in June increased to 50 and then to 80 in July) which have undergone unilateral cataract extraction and implantation of a monofocal intraocular lens.

Patients are separated into cohorts of 10 patients each; three dosing ranges (4.0 mA-min, 9.0 mA-min and 14.0 mA-min) with the two highest doses at two different treatment schedules (on day 0, day 1 and day 2 or day 0, day 1 and day 4). All three doses have the potential to add another treatment on day 7. Primary endpoint is the proportion of subjects with ACC count of zero on day 14. Secondary efficacy endpoint is the proportion of subjects with a pain score of zero on Day 7.

The top-line data announced in early August was encouraging and relates to 40 patients (4 cohorts) which were administered iontophoretic EGP-437 at either 9.0 mA-min or 14.0 mA-min on day 0, day 1 and day 2 or day 0, day 1 and day 4, with potential for an additional treatment at day 7 in all cohorts. Results showed patients receiving the

14.0 mA-min dose on days 0, 1 and 4 had the most significant improvement in ACC - with 40% of patients in this group achieving an ACC count of 0 at day 14 (i.e. the primary endpoint) and this increased to 88% on day 28.

In addition all patients receiving the iontophoretic treatment reported reduced pain at all time points with 90% having no pain as early as day 1 and increasing to 100% on day 14. In addition there was no steroid-related increase in intraocular pressure reported.

EYEG expects to enroll three additional cohorts at other doses and dosing regimens with the expectation of further improving on the efficacy data to-date. They hope to have top-line data from these additional cohorts in Q4 of this year and, assuming positive results, expects to initiate a randomized, placebo-controlled clinical trial of EGP-437 in cataract surgery patients by year-end.

Similar to macular edema, we view cataract surgery as a considerably attractive market than that of anterior uveitis given its relatively large size (i.e. ~3 million U.S. surgeries each year). We expect the upcoming interim data to provide more insight into the potential utility of EGP-437 combination treatment in a potential cataract surgery indication.

Jade Therapeutics
In early March EyeGate announced the acquisition of Jade Therapeutics, a Utah-based, privately-held specialty pharma developing locally administered, polymer-based ophthalmic therapies. Their lead technology, CMHA-S, is a proprietary cross-linked, thiolated (with carboxymethyl groups) version of hyaluronic acid (HA). HA is a naturally occurring in the human body and is a primary contributor of cell proliferation with wound-healing, tissue repair and anti-inflammatory properties. BioTime Inc. granted Jade a worldwide exclusive license to CMHA-S for delivery of any and all therapeutic molecules related to the human eye. BioTime retains rights for non-ophthalmic indications.

Terms of the deal:

- EYEG paid up to $300k of Jade's liabilities
- EYEG issued ~766k common shares to Jade, 90% which were issued at closing with the other 10% to be issued 18 months later
- An additional $2.2M in cash is payable upon receiving FDA approval of a Jade product candidate

EYEG assumed Jade's Salt Lake City based R&D facility. Jade's co-founders as well as its research team also migrated over to EyeGate. This includes their Chief Medical Officer (who assumed the same role at EYEG) and co-founder, a board certified ophthalmologist with a strong research background and who at a previous role as Pfizer's Senior Medical Director led the successful European regulatory filing for pediatric Xalatan (eye drop for open-angle glaucoma). Also coming from Jade is their head of R&D who has extensive experience in hydrogels for wound healing and drug delivery as well as another of Jade's co-founders.

EYEG pulled the trigger on Jade given the complementary product portfolios. We think this is about as good of a marriage in terms of fit for products and customer-channels that could be hoped for. And both companies' products address the shortcomings of the way that ophthalmic medications are administrated – that is, a rigorous dosing regimen and ineffective penetration.

EYEG bolts on several potential ophthalmic indications at a reasonable purchase price. And we think EyeGate OBG is already de-risked to an extent given the long history of HA being used in human eyes and its broad use and extensive successful testing for corneal repair in animals. A similar cross-linked formulation is already 510(k)-cleared for dermal wound management (BioTime's product), CMHA-S has been vigorously and successfully tested in animals and an identical composition is marketed by BayerDVM (animal health) in the U.S. and Europe under the Remend brand for corneal wound repair which has sold over 600k units. As such, this provides an almost unprecedental level of confidence in the potential for positive results of EYEG's upcoming clinical studies.

Jades Technology…
The average person has about 15 to 20 grams of hyaluronic acid in their body. It is a main component in synovial fluid, which reduces friction between joints, is found in connective tissue and is also a major component of skin where it is involved in tissue repair. It has been used since the 1970s during intraocular surgery to protect the corneal endothelium where it is still considered standard of care. Hyaluronic acid's efficacy in protecting the corneal

endothelium during cataract surgery has been well established.[9] It is also used in Europe as a first-line treatment for dry eye disease. HA is also an active ingredient in many of the "artificial tears" products sold in the U.S. and internationally. HA is also used in other applications, including as an injectable to treat osteoarthritis. Safety of HA, therefore, has already been well-established (particularly in ophthalmic applications).

One issue that HA suffers from, however, is that it has short half-life with approximately one-third of it degraded (and replenished) in the body each day. But by cross-linking it, it stabilizes the molecule and forms into a hydrogel with a very high molecular weight and viscosity which resists degradation and allows it to adhere to the surface of the eye much longer. Unlike typical eye drops, which quickly run down the side of user's face, a hydrogel will stay in place and provide the benefit of sustained release, thereby improving efficacy. It also means a much less rigorous dosing regimen. And it remains biocompatible, will thin with blinking and a user's vision will not be compromised immediately following administration (despite its gel-like properties).

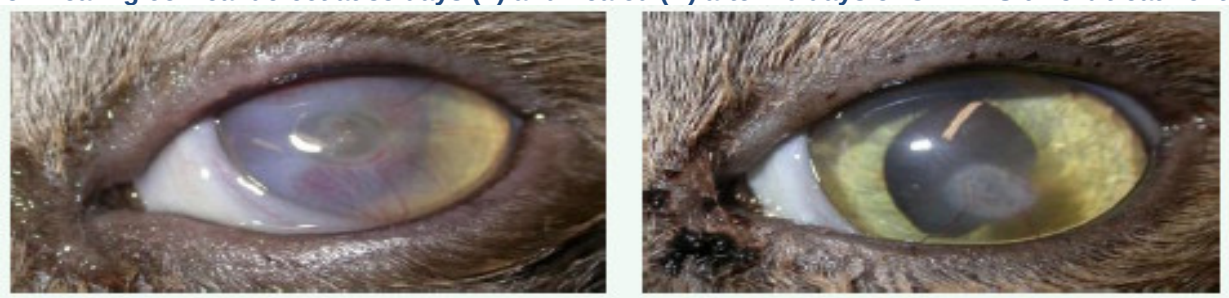
The compound starts with HA from Novosymes (bacterial fermentation). Carboxymethyl groups at then added to produce CMHA which are then thiolated using a proprietary method to produce CMHA-S. Depending on the intended application, it can be formulated into a relatively low viscosity liquid or higher viscosity gel or film.

Initial Indication…
The initial indication EYEG expects to seek is for corneal repair with EyeGate Ocular Bandage Gel', or OBG (initially JDE-003) for populations such as;

- Persistent corneal epithelial defects (PCED)
- Following photoreactive keratectomy (similar to LASIK)
- Moderate-to-severe dry eye
- Following diabetic vitrectomy (eye surgery to remove vitreous gel)

JDE-003 uses cross-linked 0.75% HA solution. A non-healing corneal defect is considered persistent, or non-healing, if it persists for more than two weeks. PCED's can result in corneal ulcers, scarring, infection and, eventually, blindness if not effectively treated. A masked, randomized study in 29 cats with superficial, mid-stromal and deep stromal (i.e. non-healing) corneal defects showed superior efficacy of CMHA-S (0.75% concentration) as compared to non-cross-linked 0.25% eye drops. Both arms received their respective eye drops 3x/day and were evaluated weekly. Primary endpoint was lack of staining with fluorescein (i.e. healed ulcer). Results showed eyes treated with CMHA-S 0.75% took an average of 21 days (± 11 days) to heal while those treated with non-cross-linked 0.25% HA concentration took an average of 32 days (± 10 days) to heal.

Non-healing corneal defect at 35 days (L) and healed (R) after 10 days of CMHA-S 0.75% treatment[10]



Non-healing corneal defect at 42 days (L) and healing (R) after 12 days of CMHA-S 0.75% treatment



[9] Goa KL, Benfield P. Hyaluronic acid. A review of its pharmacology and use as a surgical aid in ophthalmology, and its therapeutic potential in joint disease and wound healing. Drugs. 1994 Mar;47(3):536-66.
[10] Jade Therapeutics, Eyegate Pharmaceuticals

FDA Meeting Upcoming…
EYEG believes OBG will be able to follow an FDA medical device pathway (as opposed to drug pathway) and expects to meet with the agency in Q3 of this year for confirmation. We note that AmbioDisk and Prokera, both amniotic membranes (i.e. disks placed on the eye by clinicians) indicated for use of non-healing epithelial defects also did not follow NDA pathways. Prokera followed 510(k) as a Class II device while AmbioDisk is regulated under Section 361 of the Public Health Service Act by FDA with no clearance required. These are more invasive and require much greater skill to administer than eye drops or gel. This, combined with the strong safety data to-date, may play in EYEG's favor. Assuming they get confirmation of the device pathway, EYEG expects to initiate clinical studies for corneal repair in Q4.

Pipeline Indications…
In addition to corneal repair, the pipeline includes JDE-002, an ocular surface shield and JDE-004, for treatment of bacterial keratitis. Both of these programs have been funded by federal government grants.

The ocular shield candidate consists of a thin film, shaped to surface of the eye which will remain in place up to 7 days to promote healing. Department of Defense funding has funded over $1M for Phase 1 and 2 (through August 2017).

JDE-004 utilizes the Jade technology to deliver antibiotics to the eye to treat bacterial keratitis (infectious corneal ulcers), which is most common due to wearing contact lenses overnight. Typical treatment is antibiotics delivered via drops such as Bausch+Lomb's Besivance (besifloxacin 0.6%). JDE-004 would deliver the medication via a CHMA film with a 7 – 8 day release window, thereby eliminating the need of the rigorous 3x/day for 7 days dosing schedule recommended with Besivance. Jade has demonstrated safety and tolerability of the sustained release film in rabbit models.

Product #	Product	Type of Product	Indication	Formulation	Preclinical Development	IND/IDE
JDE-003	Device	Thiolated-HA Topical Drop (0.75%)	Corneal Repair	US-IDE/PMA Regulatory Pathway		
JDE-001	Drug	Thiolated-HA Topical Drop (0.4%)	Dry Eye Disease (DED)	US-IND Regulatory Pathway		
JDE-002*	Device	Thiolated-HA Ocular Surface Shield	Corneal Protection / Repair	US-IDE/PMA		
JDE-004*	Drug	Antibacterial Film	Bacterial Keratitis	IND Pathway		
JDE-005*	Drug	rHGH Film	Persistent Corneal Epithelial Defects	Orphan Drug Designation		
JDE-006	Drug	Anti-angiogenic	Corneal Neovascularization, AMD/DME	Drug Delivery Program		

*These programs are fully funded by Federal Government Grants (Department of Defense and National Science Foundation)

SOURCE: EyeGate Pharm

Market Opportunity…
EyeGate OBG is considered the lead Jade candidate with PCED potentially being the most near-term opportunity. EYEG estimates PCED encompasses an annual U.S. market of approximately 125k people. Incorporating an estimated $300 per treatment cost and an average of two (i.e. one to three) treatments per patient, results in a U.S. market opportunity worth roughly $75M (i.e. - ~$40M - $115M). Other indications for JDE-003 could include post photoreactive keratectomy, moderate-to-severe dry eye and following diabetic vitrectomy which, in aggregate, could balloon the total market opportunity to over $1B – the vast majority of which would relate to dry eye, given the relatively high incidence (3 – 5 million Americans) of the condition.

Comments
Jade's pipeline looks like it could be a seamless fit to that of EYEG's – not only does it target similar customer channels but also addresses the drawbacks of current ophthalmic drug administration. OBG, the lead candidate, is

already de-risked to an extent given the long history of HA being used in human eyes and its broad use and extensive successful testing for corneal repair in animals.

Standard of care for corneal repair, including liquid eye drops, bandage soft contact lenses, pressure patching and debridement sometimes fail or require onerous dosing/administration regimens. Newer therapies, including amniotic membranes, offer the potential for greater efficacy and more rapid healing but come with drawbacks – including that some of these must be sewn in place or glued and all require a skilled clinician. These are also relatively costly ($1k - $2k per treatment).

We think the OBG program could be fairly fast moving given the existing safety data and that the FDA regulatory pathway is expected to follow that of a device. While it may be a PMA pathway (as opposed to 510(k)), the FDA clinical program could potentially be a relatively small Phase 2 study, followed by a larger (n = 100 or 200) Phase 3 study. While this is just speculation on our part, we should know more following the anticipated FDA meeting in Q3.

We have incorporated OBG into our model and using similar methodology of that for EYEG's legacy product candidates. If all goes well we think OBG could reach the market sometime in 2018. We use a 50% probability of successful launch in the U.S. and, similar to the deal with Valeant for EGP-437 for the anterior uveitis indication, assume EYEG out-licenses marketing rights. But, given that we are modeling that EYEG assumes all R&D risk, we assume a much higher royalty rate of 20% (versus "high single digits" with Valeant for EGP-437). We think there could be several interested licensors, which could include Valeant but also Allergan and Novartis. We are modeling single-digit penetration through 2022. These, however, are early assumptions and very likely to change as more information becomes available – with the most significant near-term information expected to relate to the FDA pathway and scope of requisite clinical studies.

VALUATION

Given the pre-revenue stage of EyeGate, typical valuation methodologies such as P/E, P/EG, P/S and others which require financial metrics as components are unsuitable. As such, we believe the most appropriate valuation methodology is discounted cash flow.

Our model incorporates the following assumptions:

General assumptions:

- we have discounted all modeled milestones and royalties related to each indication to account for risk of regulatory and/or commercialization failure. These respective risk discounts are subject to change based on change in risk profile (i.e. decreasing with clinical trial and regulatory progression)
- while Valeant has currently only licensed rights for the anterior uveitis indication, we assume that if and when macular edema and cataract surgery demonstrate positive results in later stage clinical trials, that Valeant will also license rights to these indications. For consistency purposes, we assume the aggregate milestones and royalty rates are the same as for anterior uveitis
- assume all sales royalties are at 8% (EYEG has disclosed the anterior uveitis indication will pay "high single digits")
- operating expenses trend higher with progression of each indication through later-stage clinical trials and related regulatory activities. Following launch, operating expenses fall as Valeant is responsible for sales and marketing and EYEG's R&D activities temper

Anterior Uveitis Indication:

- 80% probability of successful FDA approval/clearance and launch for anterior uveitis indication. All modeled milestones and royalties related to anterior uveitis are initially discounted by 20% (i.e. 1 – 0.80) to account for risk of regulatory or commercialization failure
- EYEG begins to book revenue related to AU milestones in 2017
- Receipt of FDA approval/clearance and launch in 2018 and receipt of regulatory milestones as well as additional development milestones in that same year
- $300 cost per application x 3 applications (per clinical trial protocol) = $900/patient. Cost increases at rate of inflation
- U.S. market size of ~110k, increasing at the rate of population growth. Less than 1% penetration through 2019, mid-single digit penetration by 2023 and 10% in 2026 (the out-year in our 10-yr DCF model)

Macular Edema Indication:

- 50% probability of successful FDA approval/clearance and launch for macular edema indication. All modeled milestones and royalties related to macular edema are initially discounted by 50% to account for risk of regulatory or commercialization failure
- Receipt of development milestones begins in 2017
- Receipt of FDA approval/clearance and launch in 2020 and receipt of regulatory milestones as well as additional development milestones in that same year
- $300 cost per application x 3 applications (per clinical trial protocol) = $900/patient. Cost increases at rate of inflation
- U.S. market size of ~660k, increasing at the rate of population growth. Less than 1% penetration in 2020, mid-single digit penetration by 2023 and 12% in 2026

Cataract Surgery Indication:

- 15% probability of successful FDA approval/clearance and launch for cataract surgery indication. All modeled milestones and royalties related to cataract surgery are initially discounted by 85% to account for risk of regulatory or commercialization failure
- Cataract surgery may be the indication which the risk discount could be reduced the most significantly in the near term. Positive results from the pilot study (additional top-line data expected Q4 2016) could prompt this haircut reduction, which could positively influence our valuation of the company
- Receipt of development milestones begins in 2017

- Receipt of FDA approval/clearance and launch in 2018 and receipt of regulatory milestones as well as additional development milestones in that same year
- $300 cost per application x 2 applications (per clinical trial protocol) = $600/patient. Cost increases at rate of inflation
- U.S. market size of ~1.1M, increasing at the rate of population growth. Less than 1% penetration in 2018, mid-single digit penetration by 2021/2022 and 15% in 2026

Key Initial Assumptions

	Probability of success	Year of launch	Treatment cost	Market size ('000s)	Penetration		
					< 1%	Mid-Single	Yr 2026
Anterior Uveitis	80%	2018	$900	110	2019	2023	10%
Macular Edema	50%	2020	$900	660	2020	2023	12%
Cataract Surgery	15%	2018	$600	1,100	2018	2021/2022	15%

Jade's Pipeline
- 50% probability of successful FDA approval/clearance of OBG
- Out-licenses to major ophthalmology-focused company such as Allergan, Novartis or Bausch+Lomb for 20% of net revenues
- U.S. launch in 2018, single digit penetration through 2022
- Annual U.S. market for PCED of ~$125M
- Currently do not model other indications for OBG or for other of Jade's candidates. This will be updated with news flow

DCF Currently Values EYEG at $6/Share, Progression Through Clinicals Should Push Value Higher…
The above assumptions along with other inputs in our DCF including a 10% discount rate and 2% terminal growth rate, results in a current DCF-generated valuation of approximately $6/share. While we have incorporated some assumed revenue from Jade's pipeline, we have also incorporated assumed expenses from combining the two companies as well as R&D expenses related to the pipeline (as well as additional outstanding shares). While our $6/share target represents attractive upside to the current share price, our calculated value should appreciate further on progression of EGP-437 and Jade's pipeline through clinical trials in any of the indications as this would positively affect (i.e. decrease) our risk discounts.

FINANCIAL MODEL

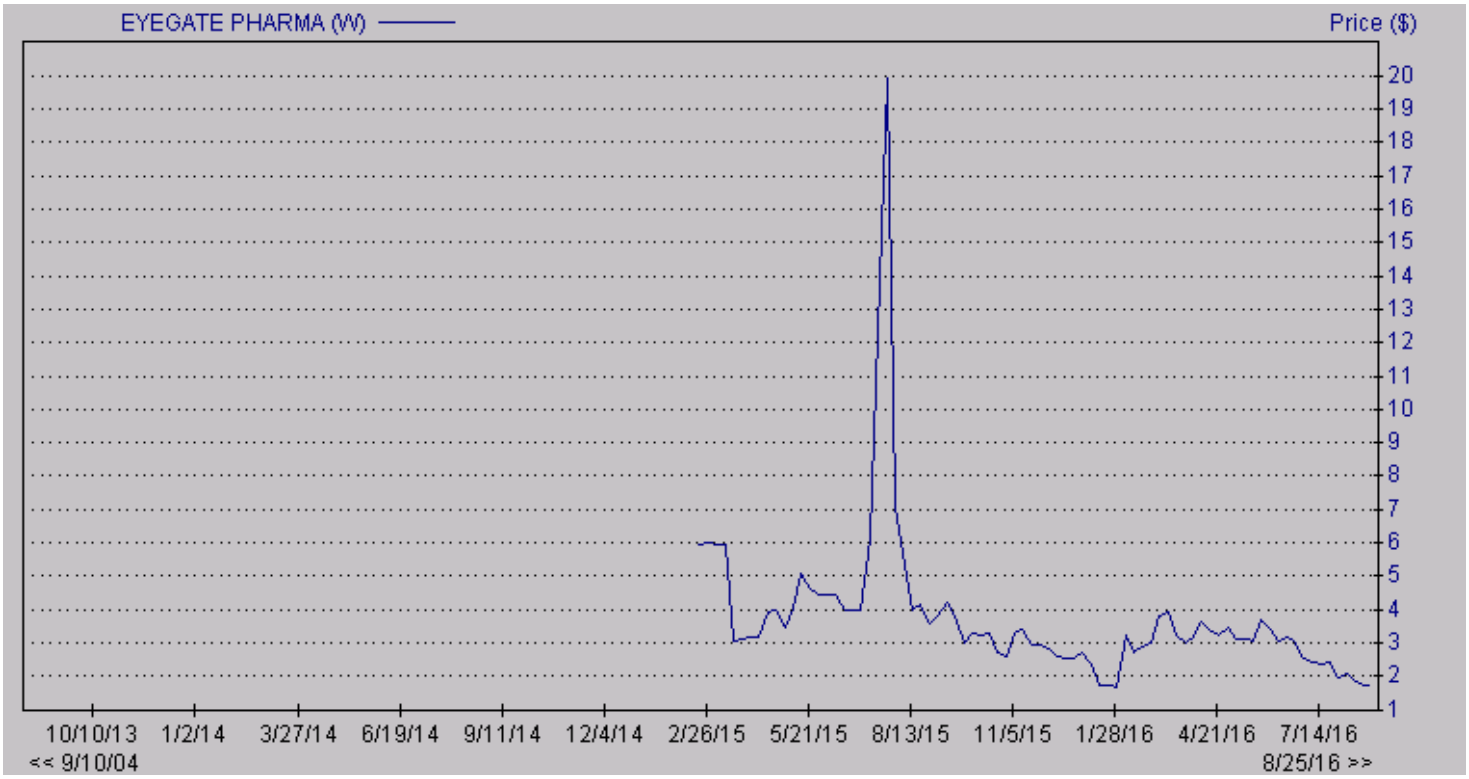
EyeGate Pharmaceuticals Inc. (figures in 000s of $)

	2015 A	Q1A	Q2A	Q3E	Q4E	2016 E	2017 E	2018 E	2019 E
Legacy Eyegate									
Anterior Uveitis									
Probability reaches market	-	-	-	-	-	80%	80%	80%	80%
U.S. Market Size	-	-	-	-	-	110,000	112,200	114,444	116,733
Penetration %	-	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.7%
Number of patients	-	-	-	-	-	**0**	**0**	**343**	**817**
EYEG Royalty rate	-	-	-	-	-	8%	8%	8%	8%
Cost per procedure	-	-	-	-	-	$900	$923	$946	$969
Revenue (000's) w/haircut	-	-	-	-	-	**$0.00**	**$0.00**	**$20.78**	**$50.69**
Milestones w/ haircut	-	-	-	-	-	**$0.00**	**$4,000.00**	**$5,600.00**	**$2,800.00**
AU Total Revenue	-	-	-	-	-	**$0.0**	**$4,000.0**	**$5,620.8**	**$2,850.7**
Macular Edema									
Probability reaches market	-	-	-	-	-	50%	50%	50%	50%
U.S. Market Size	-	-	-	-	-	660,000	673,200	686,664	700,397
Penetration %	-	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Number of patients	-	-	-	-	-	**0**	**0**	**0**	**0**
EYEG Royalty rate	-	-	-	-	-	8%	8%	8%	8%
Cost per procedure	-	-	-	-	-	$900	$923	$946	$969
Revenue (000's) w/haircut	-	-	-	-	-	**$0.00**	**$0.00**	**$0.00**	**$0.00**
Milestones w/ haircut	-	-	-	-	-	**$0.00**	**$1,250.00**	**$1,250.00**	**$2,500.00**
ME Total Revenue	-	-	-	-	-	**$0.0**	**$1,250.0**	**$1,250.0**	**$2,500.0**
Cataract Surgery									
Probability reaches market	-	-	-	-	-	15%	15%	15%	15%
U.S. Market Size	-	-	-	-	-	1,100,000	1,122,000	1,144,440	1,167,329
Penetration %	-	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%	1.7%
Number of patients	-	-	-	-	-	**0**	**0**	**2,289**	**19,845**
EYEG Royalty rate	-	-	-	-	-	8%	8%	8%	8%
Cost per procedure	-	-	-	-	-	$600	$615	$630	$646
Revenue (000's) w/haircut	-	-	-	-	-	**$0.00**	**$0.00**	**$17.31**	**$153.87**
Milestones w/ haircut	-	-	-	-	-	**$0.00**	**$375.00**	**$750.00**	**$525.00**
CS Total Revenue	-	-	-	-	-	**$0.0**	**$375.0**	**$767.3**	**$678.9**
Product Sales/Royalites	-	-	-	-	-	$0.0	$0.0	$38.1	$204.6
Dvlpmnt / Reg Milestones	-	-	-	-	-	$0.0	$5,625.0	$7,600.0	$5,825.0
Jade's Pipeline									
JDE-003 (Corneal Repair)									
Probability reaches market	-	-	-	-	-	50%	50%	50%	50%
U.S. Market Size	-	-	-	-	-	125,000	127,500	130,050	132,651
Penetration %	-	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.0%	3.0%
Number of patients	-	-	-	-	-	**0**	**0**	**1,301**	**3,980**
EYEG Royalty rate	-	-	-	-	-	20%	20%	20%	20%
Cost per procedure	-	-	-	-	-	$450	$461	$473	$485
Net Revenue (000's) w/haircut	-	-	-	-	-	**$0.00**	**$0.00**	**$59.03**	**$185.13**
Milestones w/ haircut	-	-	-	-	-	**$0.00**	**$0.00**	**$0.00**	**$0.00**
Corneal Repair Total Revenue	-	-	-	-	-	**$0.0**	**$0.0**	**$59.0**	**$185.1**
Total Milestones		-	-	-	-	$0	$5,625	$7,600	$5,825
Collaboration Revenue (Jade, Gov't		$0	$235	$203	$203	$641	$812	$0	$0
Total Revenues	$0.0	$0.0	$234.6	$203.0	$203.0	$640.6	$6,437.0	$7,697.1	$6,214.7
YOY Growth	-	-	-	-	-	-	*904.8%*	*19.6%*	*-19.3%*
Cost of Revenues	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.00	$0.0	$0.0
Gross Income	$0.0	$0.0	$234.6	$203.0	$203.0	$640.6	$6,437.0	$7,697.1	$6,214.7
Gross Margin	-	-	-	-	-	-	-	-	-
R&D	$2,717.1	$914.0	$2,481.5	$2,512.0	$2,316.0	$8,223.5	$8,644.0	$9,178.0	$9,210.0
%R&D	-	-	*1057.8%*	*1237.4%*	*1140.9%*	*1283.7%*	*134.3%*	*119.2%*	*148.2%*
SG&A	$3,960.5	$1,528.8	$1,579.2	$1,618.0	$1,708.0	$6,433.9	$6,915.0	$7,391.0	$7,603.0
%SG&A	-	-	*673.1%*	*797.0%*	*841.4%*	*1004.4%*	*107.4%*	*96.0%*	*122.3%*
Operating Income	($6,677.6)	($2,442.8)	($3,826.1)	($3,927.0)	($3,821.0)	($14,016.8)	($9,122.0)	($8,871.9)	($10,598.3)
Operating Margin	-	-	*-1630.9%*	*-1934.5%*	*-1882.3%*	*-2188.1%*	*-141.7%*	*-115.3%*	*-170.5%*
Total, other income (exp)	($1,710.4)	$0.3	$2.8	$3.2	$1.4	$7.7	$0.0	$0.0	$0.0
Pre-Tax Income	($8,388.0)	($2,442.4)	($3,823.3)	($3,923.8)	($3,819.6)	($14,009.1)	($9,122.0)	($8,871.9)	($10,598.3)
Taxes	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Tax Rate	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Net Income	($16,615.2)	($2,442.4)	($3,823.3)	($3,923.8)	($3,819.6)	($14,009.1)	($9,122.0)	($8,871.9)	($10,598.3)
YOY Growth	-	-	-	-	-	-	-	-	*19.5%*
Net Margin	-	-	-	-	-	-	-	-	-
EPS	($2.70)	($0.31)	($0.46)	($0.44)	($0.42)	($1.64)	($0.73)	($0.59)	($0.62)
YOY Growth	*-70.7%*	*-90.4%*	*88.5%*	*1316%*	*21.7%*	*-39.2%*	*-55.5%*	*-19.0%*	*5.4%*
Diluted Shares O/S	6,164	7,847	8,375	8,952	9,000	8,543	12,500	15,000	17,000

Brian Marckx, CFA

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