Zacks Small-Cap Research

March 1, 2017

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EyeGate Pharmaceuticals (EYEG-NASDAQ)

EYEG: Several Major Development Milestones Expected in 2017

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 $7/share.

Current Price (03/01/17)	$2.61
Valuation	**$7.00**

OUTLOOK

EYEG's 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 continues to enroll – if positive will support NDA filing. Launch could happen by 2018. Out-licensing agreements recently consummated with Valeant/Bausch+Lomb for two indications. Clinicals in post-cataract surgery also progressing with positive data recently announced. Recent Jade acquisition brought complementary, de-risked pipeline. First Jade candidate (EyeGate OBG) showed promising data in pilot study. Larger study expected to commence in near-term. If efficacy is confirmed, we think eventual commercialization could be reasonably high. Our DCF model, which incorporates indication-specific risk adjustments to account for potential clinical or regulatory failure for each of the programs, currently values the shares at approximately $7. 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	**$5.10**
52-Week Low	**$1.11**
One-Year Return (%)	**-30.37**
Beta	**3.21**
Average Daily Volume (sh)	**989,513**
Shares Outstanding (mil)	**10**
Market Capitalization ($mil)	**$27**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**4**
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 2017 Estimate	**N/A**
P/E using 2018 Estimate	**N/A**
Zacks Rank	**N/A**

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

ZACKS ESTIMATES

Revenue
(in 000s of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2016	0 A	235 A	274 A	160 A	669 A
2017	220 E	225 E	2000 E	2000 E	4445 E
2018					8680 E
2019					4994 E

Earnings per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2016	-$0.31 A	-$0.46 A	-$0.36 A	-$0.38 A	-$1.51 A
2017	-$0.35 E	-$0.33 E	-$0.18 E	-$0.17 A	-$0.99 E
2018					-$0.57 E
2019					-$0.67 E

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

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Q4 Financial Results, Operating Update…

On February 23rd EyeGate reported financial results for their fourth quarter ending December 31st. The company reported an additional $160k of collaboration revenue related to government grants which are funding some of Jade's pipeline candidates. In September 2016 EYEG announced that they were awarded an additional $448k from the U.S. Department of Defense, which represents the second year of funding under an SBIR grant related to the development of CMHA-S as an ocular bandage ("OBG"). Approximately $445k remains under the current grants which run through 2017 and which is reflected in our model as revenue in the current year.

Q4 operating expenses were $3.9M, up slightly from the $3.6M in Q3 but below our $4.1M estimate. The difference from our estimate relates to lower SG&A expense. Meanwhile, R&D continues to trend at about $2.5M, which includes 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. Additionally, the OBG pilot study in PRK recently completed.

We continue to expect operating expenses to grow throughout 2017 with additional activity in the aforementioned programs. EYEG expects the phase 3 anterior uveitis study, which continues to enroll, to complete later this year while a new phase 2 cataract surgery study is expected to commence in 2017. Management also anticipates initiating a controlled clinical trial of OBG in the first half of this year.

Q4 net loss and EPS were $3.7M and ($0.38), compared to our $3.9M and ($0.42) estimates.

Cash: Cash balance at 2016 year end was approximately $3.6M which, in addition to cash expected to receive through 1H, EYEG believes is sufficient to fund operations for approximately five months. In February 2017 EYEG authorized the restart of the at-the-market equity program for sales of up to $3.6M (gross). We also note that earlier this month the company entered into a licensing agreement with Valeant Pharmaceuticals, terms of which call for Valeant to pay EYEG $4M upfront.

Cash used in operating activities in the three and twelve months ending 12/31/16 was $2.1M ($3.6M ex-changes in working capital) and $8.4M ($12.8M ex-changes in working capital).

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

EYEG's Anticipated Near-Term Milestones Include:

- **OBG**
  - Initiate ph 2 study in Q2 2017
  - de novo 510(k) filing for corneal re-epithelization by year-end 2017
  - OBG CE Mark by year-end 2017, European launch in Q1 2018
- **EGP-437**
  - Uveitis
    - Top-line data from ph 3 anterior uveitis confirmatory study in Q3 2017
    - NDA filing for uveitis by year-end 2017
  - Cataract surgery
    - Initiate ph 2 trial in Q2 2017
    - Assuming positive ph 2 results, would follow with a ph 3 study
    - Supplementary NDA related to pain and inflammation following ocular surgery in 2H 2018

EGP-437: Cataract Surgery

The most recent significant news was last week's announcement that Valeant picked up their option to license rights to EGP-437 for cataract surgery.

Valeant Picks Up Cataract Surgery Licensing Option: EYEG Gets $4M + Potential $99M

In July 2015 EYEG licensed manufacturing and commercialization rights of their EGP-437/EyeGate Delivery System combination product for uveitis to Valeant Pharmaceuticals (VRX) in return for $1M upfront cash, another potential (up to) $32.5M in development, regulatory and sales milestones, and high single digit royalties on sales. Valeant also received an option of last refusal to license EYEG's combination product for any other indications.

Valeant picked up that option for the cataract surgery indication – terms of which are very similar, although potentially more lucrative to EYEG, to the uveitis licensing agreement. Last week EYEG announced that in return for $4M upfront cash and up to an additional potential $99M in development and commercialization milestones, they licensed rights to their EGP-437/delivery combination product candidate for the treatment of post-operative pain and inflammation in ocular surgery patients.

Key points of the agreement include;

- EYEG
  - Receives:
    - $4M upfront cash
    - up to ~$99M upon achievement of specific (undisclosed) development/commercialization milestones
    - royalties (undisclosed rate) on net sales, if and when FDA cleared and commercialized
  - Is responsible for
    - further development, and related cost, of the product for this indication
    - obtaining FDA regulatory marketing clearance
    - 50% of the cost of any FDA-mandated post-marketing studies or related development, if required
- Valeant
  - Receives:
    - exclusive right to manufacture and commercialize the product for this indication throughout the world
    - exclusive right to develop the product for this indication outside the U.S.
    - right of last refusal for any future indications that EYEG seeks to commercialize the product for
  - Is responsible for:
    - Cost of developing the product, including regulatory costs, for this indication outside the U.S. if VRX chooses to do so
    - 50% of the cost of any FDA-mandated post-marketing studies or related development, if required

Our comments:

As we noted following the initial licensing agreement covering the uveitis indication, Valeant, through their Bausch + Lomb subsidiary, provides EYEG with seamless entry into the difficult-to-penetrate ophthalmic therapy market. These licensing deals also provide non-dilutive upfront operating and product development capital and, along with development-related milestones, greatly mitigate financial and product development risk. And, we think the fact that Valeant came back and exercised their future-indication option indicates provides additional and substantive validation of the potential utility, versatility and clinical efficacy of the EGP-437 combo product.

EYEG and VRX did not disclose certain details of these agreements including the specific development and commercial milestone triggers or the royalty rate on sales. This makes it difficult to forecast/model the related potential revenue contribution to EYEG. Even the $1M upfront cash payment that EYEG received in Q3 2015 (along with additional subsequent progress payments) for the uveitis indication has yet to be booked to revenue but instead remains on the balance sheet as deferred income (EYEG does note in their 2016 10-K, however, that they expect to begin recognizing revenue related to the uveitis licensing agreement in development progress payments during in 2017 and did disclose more info about the AU-related milestones). As such, our model is highly subject to change based on things like the timing of when the $4M upfront payment for cataract surgery is realized – the particularly timing of which is largely immaterial (i.e. EYEG has the cash).

Positive Phase Ib/IIa Data

In December 2015 EYEG announced additional positive clinical data from their phase Ib/IIa post-cataract surgery dose-ranging clinical trial. As a reminder, the study was designed to **enroll up to 80 patients** which have undergone unilateral cataract extraction and implantation of a monofocal intraocular lens.

Patients were separated into cohorts of 10 patients each with each cohort treated at different doses and/or treatment regimens. Subjects were evaluated on days 1 (i.e. 1 day following cataract surgery), 14 and 28. Primary endpoint was the proportion of subjects with ACC count of zero on day 14. Secondary efficacy endpoint was the proportion of subjects with a pain score of zero on Day 7.

In August 2016 EYEG announced top-line data from 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.

Concurrent with the top-line data release in August, the company noted that they would enroll three additional cohorts at other doses and dosing regimens with the expectation of further improving on the efficacy data to-date.

In December 2016, EYEG announced additional positive data. Dosing and treatment regimen were modified slightly from that of the cohorts represented in the August data and included 30 patients (3 cohorts) which were administered iontophoretic EGP-437 at either 4.5mA-min on day 0 (post-operative), day 1 and day 4 or at 14mA-min on day 0 (pre-operative), day 1 and day 4. The third cohort was dosed with placebo on day 0 (post-operative), day 1 and day 4. An optional treatment (at physician's discretion) on day 7 was available for all three cohorts.

Results indicated that subjects in the lowest dose cohort (i.e. 4.5mA-min) exhibited the greatest response, with 30% of those patients reaching an ACC count of zero by day 14 and 80% by day 28. While there was limited other data released, EYEG's press release (http://bit.ly/2ma3fli) did provide other indications of a positive EGP-437 treatment response including that; ACC count reduction was observed in both EGP-437 treatment arms, only 10% of placebo patients reached an ACC count of zero by day 28 and 80% of placebo patients required rescue prior to day 14.

In addition, and related to the pain outcome measure, it was noted that all EGP-437 patients experienced less pain at all time points and 70% had pain score of zero by day 1 whereas only 10% of placebo patients had pain score of zero at day 1.

See our table below summarizing the results disclosed in August (4 cohorts) and December (3 cohorts) and the respective dosing and treatment regimens. Perhaps interesting, and maybe arguably confounding, is that ACC count reduction was most profound in one of the two highest dose cohorts in the August data but the December data showed the opposite – that is, the lowest dose cohort had the greatest number of subjects reaching an ACC count of zero.

Although not mentioned in EYEG's data announcement, one potential factor that could relate to this seeming counter-dose effect is that the higher dose cohort (i.e. 14mA-min) in the December data was treated on day 0 pre-operatively while the lower dose cohort (i.e. 4.5mA-min) was treated post-operatively on day 0. Treating pre-operatively was found to be problematic in EYEG's earlier cataract surgery (completed in 2013) study as the surgical procedure washed out the drug, thereby eliminating any potential therapeutic benefit. This "wash-out" effect is what prompted the change in trial design to where EGP-437 is administered immediately following surgery.

We characterize this data as highly promising given that it provides additional evidence of a positive treatment response to EGP-437. EYEG currently expects to initiate a phase 2b trial of EGP-437 in cataract surgery patients in Q2 2017. Assuming positive results, a subsequent single phase 3 study is expected to be sufficient to support an FDA filing. If all goes well, an FDA filing for a post-cataract surgery indication (reduction of pain/inflammation) could be made sometime next year (EYEG currently hopes to be able to make a supplemental NDA filing for a post-cataract surgery indication in 2H 2018). The recent licensing agreement with Valeant should aid in funding development.

Date	N =	EGP-437 Dose	Days Dosed	ACC Count of Zero at Day 14	ACC Count of Zero at Day 28	Additional Outcomes
8/1/2016	10	9mA-min	0,1,2, (7)*	N/A	N/A	Subjects in the 14MA-min on days 0,1 and 4 showed greatest reduction in ACC count. All patients receiving EGP-437 iontophoretic treatment experienced reduction in pain at all time points with 90% having no pain at day 1, increasing to 100% on day 14.
	10	9mA-min	0,1,4, (7)*	N/A	N/A	
	10	14mA-min	0,1,2, (7)*	N/A	N/A	
	10	14mA-min	0,1,4, (7)*	40%	88%	
12/5/2016	10	4.5mA-min	0 post-op,1,4, (7)*	30%	80%	A positive response, as determined by reduction in ACC count, was observed in both EGP-437 treatment arms with 4.5mA-min (3.0 ma for 1.5 mins) showing greatest response. 80% of patients in placebo cohort required rescue prior to Day 14 and only 10% had ACC of zero at Day 28. All EGP-437 patients experienced less pain at all time points and 70% had pain score of zero by Day 1 whereas only 10% of placebo patients had pain score of zero at Day 1.
	10	14mA-min	0 pre-op,1,4, (7)*	N/A	N/A	
	10	Placebo 14mA	0 post-op,1,4, (7)*	N/A	10%	

(7)* = optional dosing on day 7
N/A = change in ACC not disclosed

EGP-437: Anterior Uveitis

While EYEG has not provided an update on the anterior uveitis (or macular edema) studies in the last several of months, they do note in their 2016 10-K (filed Feb 23, 2017) that their phase 3 anterior uveitis clinical trial continues to enroll patients and they hope to have top-line data sometime in Q3 2017. If all goes well EYEG thinks they may be in a position to make an NDA filing for this indication by 2017 year-end. The fact that EYEG continues to receive development-related milestones from Valeant (deferred revenue balance was $4.2M at 2016 year-end, up from $3.4M at 9/30/16) also suggests this study is progressing. Below is a refresher of the ongoing phase 3 study.

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 (see Appendix for development background), will be sufficient to support an 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). Study details are listed on clinicaltrials.gov, trial ID NCT02517619

Patients are 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. The latest update on clinicaltrials.gov, on 8/2/16, lists anticipated primary completion date and last follow-up date of June 2017 and October 2017, respectively. While EYEG has not provided an update on this study in the last several months, they do note in their 10-K (filed Feb 23, 2017) that it continues to enroll patients and they hope to have top-line data

sometime in Q3 2017. If all goes well EYEG thinks they may be in a position to make an NDA filing for this indication by 2017 year-end.

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 an 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."[1] 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.

CMHA-S: Ocular Bandage Gel (OBG) Positive Initial Clinical Data, Larger Study Could Initiate Q2 2017

In late January 2017 EyeGate announced encouraging top-line results of its human pilot study of its Ocular Bandage Gel (OBG). While the study was small, results indicate that OBG may be associated with faster corneal healing following eye surgery as compared to standard of care. We view this as meaningfully positive as it sets the stage to move OBG into a larger study – which is now in the planning stage and, assuming IDE approval, could kick off in Q2.

As a reminder, OBG is the lead CMHA-S candidate which came from the Jade Therapeutics acquisition and is being developed for corneal repair indications. Given the strong safety profile of the compound and expected (relatively streamlined) de novo 510(k) FDA pathway (in November FDA confirmed de novo 510(k) is an appropriate pathway for OBG to pursue in seeking U.S. regulatory clearance), we think OBG may represent one of EYEG's most near-term commercialization opportunities. See our Appendix for more background on the compound and the Jade acquisition.

The pilot study compared OBG to artificial tears with bandage contact lens (BCL) in patients undergoing bilateral photorefractive keratectomy ("PRK"). PRK is a type of vision-correction laser eye surgery - recovery from which includes regrowth of the epithelium (i.e. thin outer layer of the cornea).

Ocular Bandage Gel photoreactive keratectomy pilot study

- Objective: evaluate safety and performance of OBG eye drop administered 4x/day for 14 days with or without a BCL as compared to artificial tears and a BCL in healing of corneal epithelial defects
- Primary efficacy endpoint: complete wound closure by Day 3
- Design: prospective, randomized, controlled study in up to 39 subjects undergoing bilateral PRK surgery. Subjects randomized to one of three cohorts;
  - Arm 1 (n=12): EyeGate Ocular Bandage Gel 4x/day for 2 weeks after surgery without a BCL
  - Arm 2 (n=14): EyeGate Ocular Bandage Gel 4x/day for 2 weeks after surgery in combination with a BCL
  - Arm 3 (n=13): Artificial tears 4x/day and BCL

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

Topline results of the pilot study, which was the first in-human study of OBG, showed a greater proportion of OBG-treated patients versus those treated with standard of care met the **primary endpoint** of complete wound closure by Day 3. Top-line results were initially announced in January but in EYEG's 2016 10-K (filed Feb 23, 2017) additional data was provided. The updated data showed that 10 of the 12 (83%) patients treated with OBG alone (i.e. no BCL) met the primary endpoint, compared to 9 of the 14 (64.3%) OBG+BCL patients and just 7 of the 13 (53.8%) artificial tears+BCL patients.

Remaining wound surface area on Days 1 (24 hours following surgery) and 3 were also assessed and similarly favored the OBG-alone cohort which had an average wound size of just 18.5mm on Day 1 and 0.02mm on Day 3. This compares to 39.5mm and 0.37mm in the SOC patients at Days 1 and 3, respectively.

	Treatment	Day 3 Wound Closure %	Surface Area Day 1	Surface Area Day 3
Arm 1 (n=12)	OBG	83.3%	18.5mm	0.02mm
Arm 2 (n=14)	OBG + BCL	64.3%	40.7mm	0.10mm
Arm 3 (n=13)	SOC*	53.8%	39.5mm	0.37mm
Delta favoring OBG		39.4%	53.2%	94.4%

* standard-of-care: artificial tears w / BCL

While specifics were not provided relative to adverse events, EYEG did note in their PR that the study demonstrated safety and tolerability.

Given the positive results of the pilot study, EYEG plans to move into a double-blinded study comparing OBG-alone (OGB monotherapy) to BCL for re-epithelialization following PRK and hopes to commence the study in Q2 of this year (following IDE approval). We look forward to hearing details about the planned design and size of this study and note that given the de-risked nature of OBG, if efficacy is confirmed in this follow-up study, we think the likelihood of eventual commercialization could at that point be reasonably high. The company is currently targeting both a 510(k) de novo filing in the U.S. and CE Marking (Europe) of OBG by current year-end.

We also think that, assuming continued success in the PRK/ re-epithelialization studies, that CMHA-S programs could reasonably be expanded to include other indications given its safety profile and potential broad applications related to corneal wound healing. And as a reminder, in addition to Ocular Bandage Gel, Jade had already initiated development programs for CMHA-S in other applications including as an ocular surface shield and for treatment of bacterial keratitis – both of which have been funded by federal grants.

VALUATION

Our model incorporates the following assumptions:

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:
- We have removed the ME indication from our model as we expect EYEG will be dedicating resources towards other programs. We will revisit the ME indication in the event EYEG continues development in ME

Cataract Surgery Indication:
- Following the announcement that Valeant will license rights for the cataract surgery indication we moved our probability of successful FDA approval/clearance and launch for cataract surgery indication up from 15% to 30%. All modeled milestones and royalties related to cataract surgery are initially discounted by 70% to account for risk of regulatory or commercialization failure
- As we had noted in prior updates, we felt that the cataract surgery could be the indication which the risk discount could be reduced the most significantly in the near term. Additional positive clinical data could prompt another reduction to the haircut
- 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

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 initial indication 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 $7/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 $7/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 $7/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 $)

	2016 A	Q1E	Q2E	Q3E	Q4E	2017 E	2018 E	2019 E
Milestones & Royalties	$0	$0	$0	$2,000	$2,000	$4,000	$8,680	$4,994
Collaboration Revenue (Jade, Gov't grants)	$669	$220	$225	$0	$0	$445	$0	$0
Total Revenues	$669.2	$220.0	$225.0	$2,000.0	$2,000.0	$4,445.0	$8,679.8	$4,993.6
YOY Growth	-	-	*-4.1%*	*629.2%*	*1147.2%*	*564.2%*	*95.3%*	*-42.5%*
Cost of Revenues	$0.0	$0.0	$0.0	$0.0	$0.0	$0.00	$0.0	$0.0
Gross Income	$669.2	$220.0	$225.0	$2,000.0	$2,000.0	$4,445.0	$8,679.8	$4,993.6
Gross Margin	-	-	-	-	-	-	-	-
R&D	$8,422.5	$2,618.0	$2,712.0	$2,888.0	$2,947.0	$11,165.0	$11,561.0	$11,339.0
% R&D	*1258.5%*	*1190.0%*	*1205.3%*	*144.4%*	*147.4%*	*251.2%*	*133.2%*	*227.1%*
SG&A	$5,593.6	$1,222.0	$1,255.0	$1,344.0	$1,401.0	$5,222.0	$6,884.0	$6,958.0
% SG&A	*835.8%*	*555.5%*	*557.8%*	*67.2%*	*70.1%*	*117.5%*	*79.3%*	*139.3%*
Operating Income	($13,346.8)	($3,620.0)	($3,742.0)	($2,232.0)	($2,348.0)	($11,942.0)	($9,765.2)	($13,303.4)
Operating Margin	*-1994.3%*	*-1645.5%*	*-1663.1%*	*-111.6%*	*-117.4%*	*-268.7%*	*-112.5%*	*-266.4%*
Total, other income (exp)	$3.4	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Pre-Tax Income	($13,343.4)	($3,620.0)	($3,742.0)	($2,232.0)	($2,348.0)	($11,942.0)	($9,765.2)	($13,303.4)
Taxes	$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%*
Net Income	($13,343.4)	($3,620.0)	($3,742.0)	($2,232.0)	($2,348.0)	($11,942.0)	($9,765.2)	($13,303.4)
YOY Growth	-	-	-	-	-	-	-	*36.2%*
Net Margin	-	-	-	-	-	-	-	-
EPS	($1.51)	($0.35)	($0.33)	($0.18)	($0.17)	($0.99)	($0.57)	($0.67)
YOY Growth	*-44.0%*	*14.0%*	*-28.1%*	*-51.8%*	*-55.7%*	*-34.7%*	*-41.8%*	*15.8%*
Diluted Shares O/S	8,834	10,201	11,400	12,700	14,100	12,100	17,000	20,000

Brian Marckx, CFA

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APPENDIX

ANTERIOR UVEITIS

Anterior Uveitis Development Background:

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^2, 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

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

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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.

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

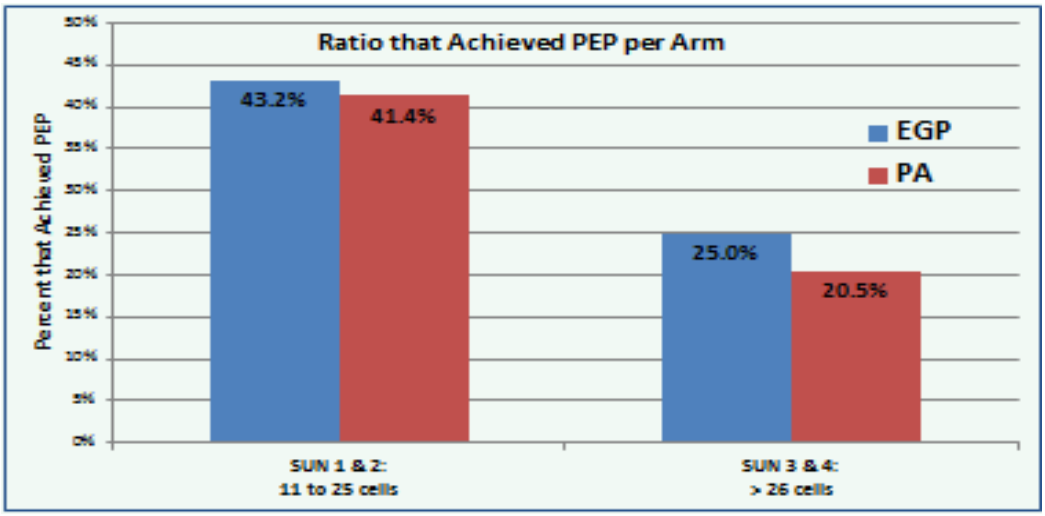
Results: (per information contained in company public filings) While response rates were similar in both the ITT and PP populations, non-inferiority (as pre-defined in the study protocol) was just missed.

- 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;

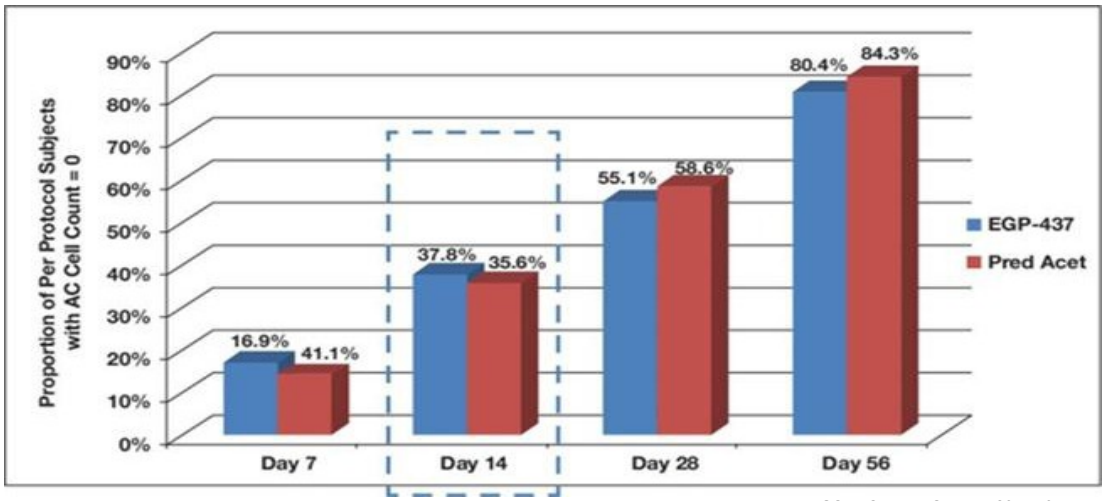
- Greater Proportion of High ACC Count Patients in EGP-437 Arm: a higher proportion of EGP-437 patients (52 of 96, or 54%) had baseline ACC counts greater than 25 as compared to those in the PA arm (40 of 97, or 41%). A post-hoc analysis was done on these high ACC count (i.e. potentially harder to treat)

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

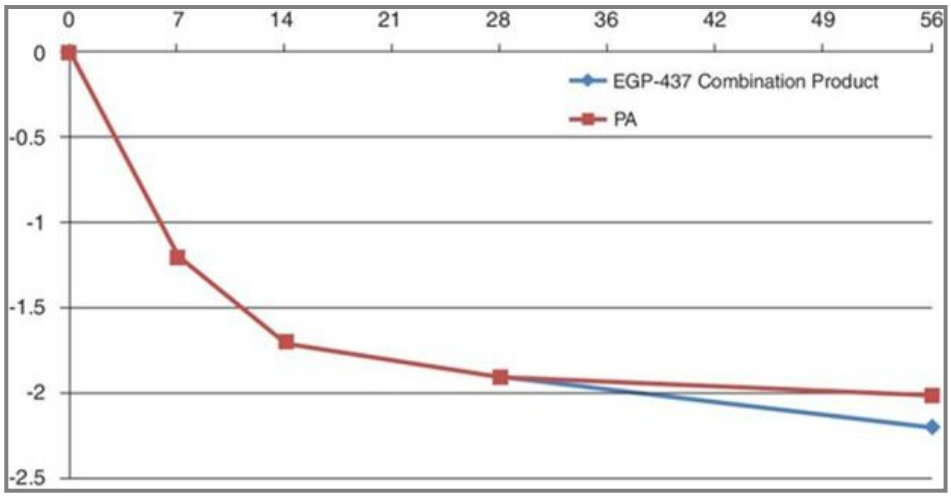
- Similar Complete Response Timeframes: "Time to anterior chamber cell count and score of zero" was a secondary endpoint. Despite the baseline difference in severity of disease (as measured by ACC count), the time to reach ACC count of zero was generally similar in both arms throughout the study (chart 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

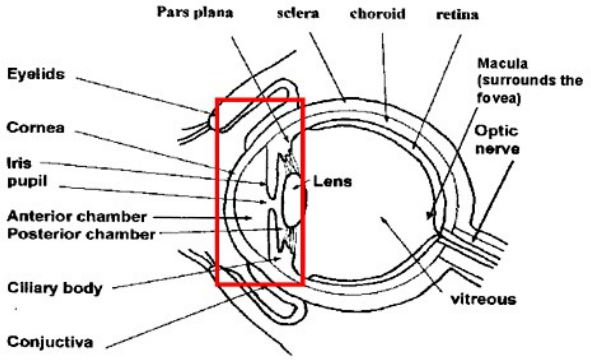
Key Takeaways:

- 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

Non-Infectious Anterior Uveitis Background

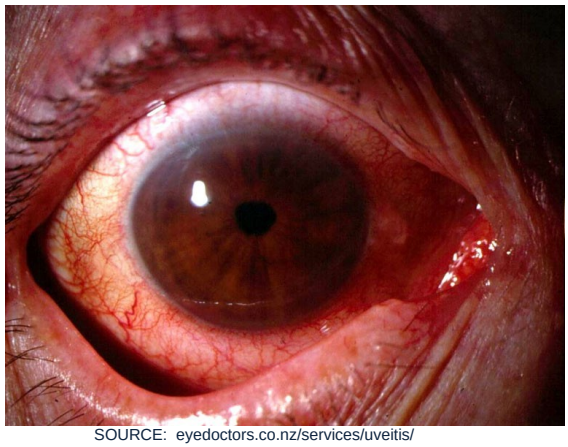
Uveitis is a generic term used to describe inflammation of the uvea. It can occur either in isolation or be the result of an underlying medical condition in other parts of the body. The uvea is the middle layer of the eye, below the white of the eye, and consists of the iris (colored portion), choroid 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[3,4,5,6] - 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

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,

[3] 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

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

[5] 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

[6] 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.

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.[7]

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.

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.

Valeant Licensing Agreement for EGP-437 in Anterior Uveitis:

The ophthalmic therapy market is fairly concentrated with only three major companies; Alcon, Allergan plc and Valeant Pharmaceuticals Bausch+Lomb division dominating the space. In July 2015 EYEG announced a licensing agreement, granting Valeant worldwide rights to manufacture and commercialize the Eyegate II Delivery System and EGP-437 for the uveitis indication as well as right of last refusal in other applications. In return, EYEG received upfront cash ($1 million) and is eligible for up to $32.5 million in development, regulatory and sales milestones. EYEG will also receive (high single digit) royalties on sales. EYEG is responsible for product development and related costs for the anterior uveitis indication in the U.S. Valeant has the right to develop the product outside of the U.S. and will be responsible for associated development costs.

This deal not only affords EYEG entry into the difficult-to-penetrate ophthalmic therapy market, but does so with some mitigated financial and product development risk. We also view this partnership with one of the ophthalmology majors as a meaningful vote of confidence in the product. In a deal valued at $8.7 billion, Valeant acquired Bausch + Lomb in 2013 in order to bolt on capabilities in the growing ophthalmology market. Bausch & Lomb, which is the largest worldwide provider of contact lenses, has a broad product line that also includes ophthalmic pharmaceuticals and ophthalmic surgical products.

Under the agreement, as EYEG makes certain predetermined development progress they receive additional progress payments from Valeant. The upfront and progress payments are initially booked as deferred revenue on EYEG's balance sheet and will be recognize these as revenue as respective milestones are completed. As of 12/31/17 EYEG' deferred revenue balance was $4.2M and they had yet to recognize any revenue from this agreement (although EYEG expects to begin recognizing revenue from this in 2017). We note that while neither Eyegate or Valeant has disclosed exactly how the milestones are structured or specifically what triggers additional development progress payments, EYEG did provide some more information in that regard in their 2016 10-K (filed Feb 23, 2017) which we have pasted below.

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

Per EYEG's 2016 10-K (Feb 23, 2017): "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 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 the Company 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 Consolidated Balance Sheet, and later in 2015 began receiving certain additional payments, based on R&D progress, to continue over several years. The Company receives payments both when it crosses certain thresholds on the way to each Milestone (each, a "Progress Payment"), as well as once it achieves each Milestone. The Company is entitled to retain all of these payments. The Company defers each Progress Payment, capitalizes each payment on its Consolidated Balance Sheet as Deferred Revenue, and recognizes these payments in the aggregate as Revenue once it achieves the Milestone to which the Progress Payment relates. The Company recognizes the initial upfront payment as Revenue ratably as it 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 all Milestones. Accordingly, the Deferred Revenue account on the Consolidated Balance Sheet is reduced as Revenue is recognized in the Consolidated Statement of Operations. The Company expects to begin recognizing Revenue with respect to the Valeant Agreement Progress Payments in 2017."

CMHA-S

Jade Therapeutics
In March 2016 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 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 was 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.[8] 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).

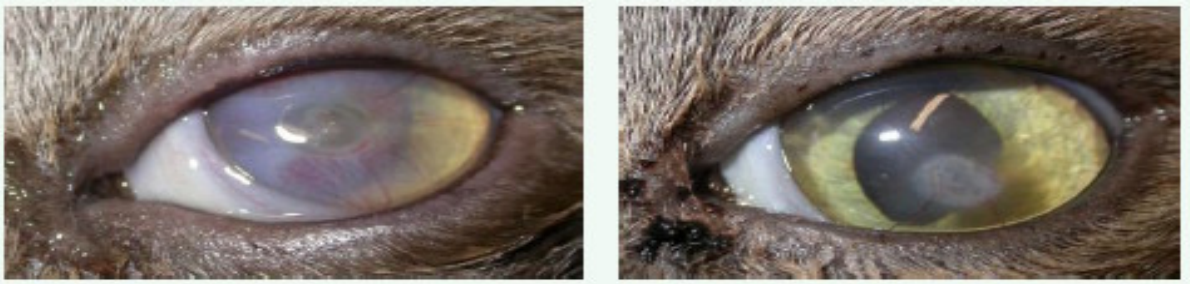
The compound starts with HA from Novosymes (bacterial fermentation). Carboxymethyl groups at then added to produce CMHA which are then thiolated using a proprietary method to produce CMHA-S. Depending on the intended application, it can be formulated into a relatively low viscosity liquid or higher viscosity 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 (or PRK, which is 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[9]



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



[8] 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.
[9] Jade Therapeutics, Eyegate Pharmaceuticals

De Novo 510(k) Pathway Confirmed…
In November 2016 EYEG announced that, following a pre-submission meeting with FDA, that the agency confirmed de novo 510(k) was an appropriate pathway for OBG to pursue in seeking U.S. regulatory clearance. While it had been our expectation that a medical device pathway would be deemed appropriate given that a similar cross-linked formulation had already followed a 510(k) route towards FDA clearance (for dermal wound management), we still view this as positive news as it confirms that EYEG will avoid having to pursue PMA. It also speaks to the validated safety profile of CMHA-S.

De Novo 510(k) was created by FDA in an effort to help streamline approval of novel, low-to-moderate risk medical devices. Prior to de novo the only route for new devices and for which there was not an acceptable predicate, regardless of their risk profile, was the relatively long, arduous and costly PMA process. The other benefit of De Novo is an expected shorter FDA review time following submission FDA s stated goal for De Novo submissions is to make a determination within 120 days while their goal with PMA is 180 days.

For reference, 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.

Positive Pilot Study Results in Corneal Epithelial Wounds Following PRK…
In late January 2017 EyeGate announced encouraging top-line results of its human pilot study of its Ocular Bandage Gel (OBG). While the study was small, results indicate that OBG may be associated with faster corneal healing following eye surgery as compared to standard of care. We view this as meaningfully positive as it sets the stage to move OBG into a larger study – which is now in the planning stage and, assuming IDE approval, could kick off in Q2.

The pilot study compared OBG to artificial tears with bandage contact lens (BCL) in patients undergoing bilateral photorefractive keratectomy ("PRK"). PRK is a type of vision-correction laser eye surgery - recovery from which includes regrowth of the epithelium (i.e. thin outer layer of the cornea).

Ocular Bandage Gel photoreactive keratectomy pilot study

- Objective: evaluate safety and performance of OBG eye drop administered 4x/day for 14 days with or without a BCL as compared to artificial tears and a BCL in healing of corneal epithelial defects
- Primary efficacy endpoint: complete wound closure by Day 3
- Design: prospective, randomized, controlled study in up to 39 subjects undergoing bilateral PRK surgery. Subjects randomized to one of three cohorts;
  - Arm 1 (n=12): EyeGate Ocular Bandage Gel 4x/day for 2 weeks after surgery without a BCL
  - Arm 2 (n=14): EyeGate Ocular Bandage Gel 4x/day for 2 weeks after surgery in combination with a BCL
  - Arm 3 (n=13): Artificial tears 4x/day and BCL

Topline results of the pilot study, which was the first in-human study of OBG, showed a greater proportion of OBG-treated patients versus those treated with standard of care met the **primary endpoint** of complete wound closure by Day 3. Top-line results were initially announced in January but in EYEG's 2016 10-K (filed Feb 23, 2017) additional data was provided. The updated data showed that 10 of the 12 (83%) patients treated with OBG alone (i.e. no BCL) met the primary endpoint, compared to 9 of the 14 (64.3%) OBG+BCL patients and just 7 of the 13 (53.8%) artificial tears+BCL patients.

Remaining wound surface area on Days 1 (24 hours following surgery) and 3 were also assessed and similarly favored the OBG-alone cohort which had an average wound size of just 18.5mm on Day 1 and 0.02mm on Day 3. This compares to 39.5mm and 0.37mm in the SOC patients at Days 1 and 3, respectively.

	Treatment	Day 3 Wound Closure %	Surface Area Day 1	Surface Area Day 3
Arm 1 (n=12)	OBG	83.3%	18.5mm	0.02mm
Arm 2 (n=14)	OBG + BCL	64.3%	40.7mm	0.10mm
Arm 3 (n=13)	SOC*	53.8%	39.5mm	0.37mm
Delta favoring OBG		39.4%	53.2%	94.4%

* standard-of-care: artificial tears w / BCL

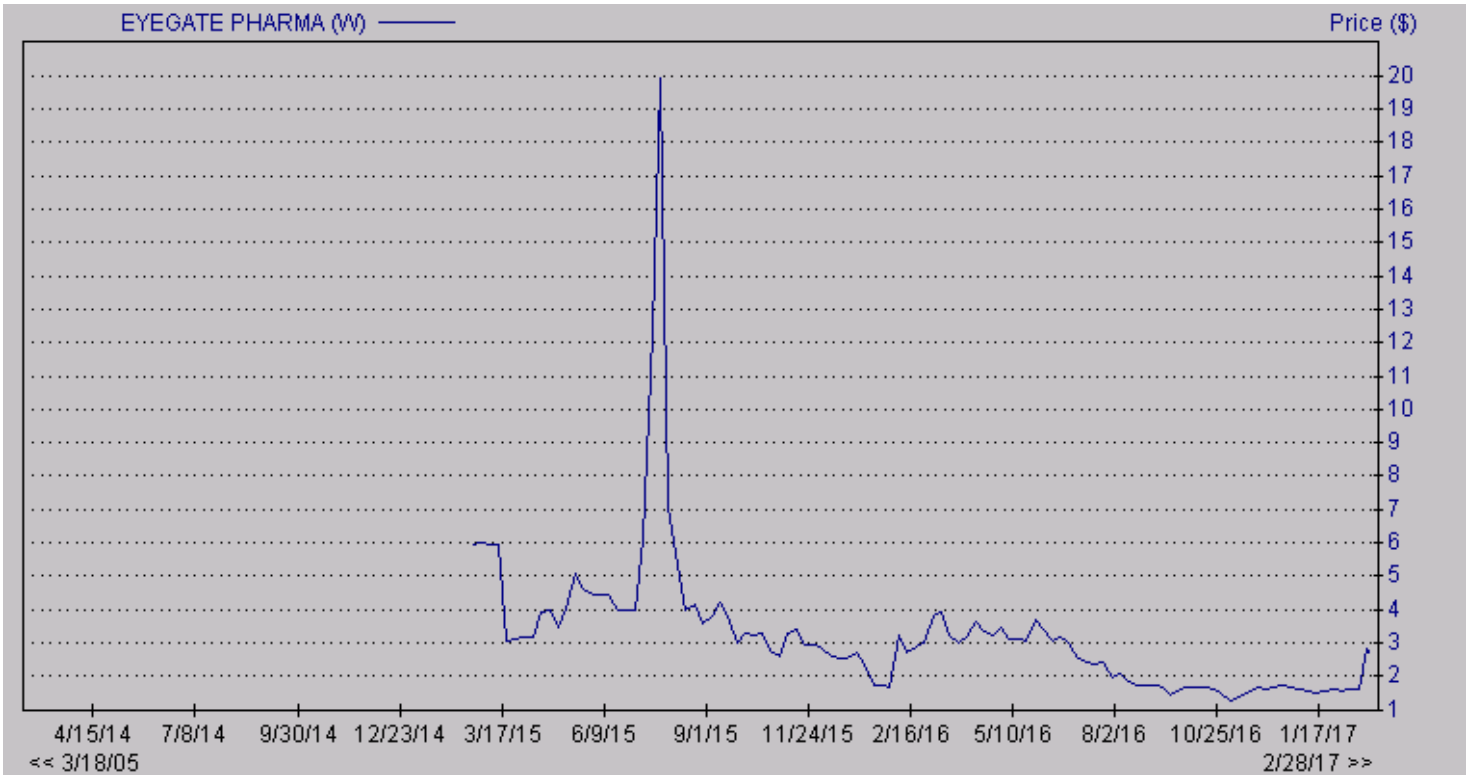
While specifics were not provided relative to adverse events, EYEG did note in their PR that the study demonstrated safety and tolerability.

Given the positive results of the pilot study, EYEG plans to move into a double-blinded study comparing OBG-alone (OGB monotherapy) to BCL and hopes to commence the study in Q2 of this year (following IDE approval). We look forward to hearing details about the planned design and size of this study and note that given the de-risked nature of OBG, if efficacy is confirmed in this follow-up study, we think the likelihood of eventual commercialization could at that point be reasonably high. The company is currently targeting both a 510(k) de novo filing in the U.S. and CE Marking (Europe) of OBG by current year-end.

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.

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.

HISTORICAL ZACKS RECOMMENDATIONS



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