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Zacks Small-Cap Research

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EyeGate Pharmaceuticals (EYEG-NASDAQ)

EYEG: Ph3 Anterior Uveitis Study Completes Enrollment, Delays Continue With OBG Programs

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 $3.00/share.

Current Price (04/10/18)	$0.33
Valuation	**$3.00**

OUTLOOK

EGP-437 anterior uveitis phase III study hit the 75% mark in December (a Valeant-milestone triggering event) and completed in early April (another Valeant-milestone triggering event). Unfortunately the OBG programs have experienced ongoing delays as the company continues to work to get IDE approval to commence a second pilot study in (their initial target indication of) post-PRK surgery. EYEG addressed FDA's initial requests in an IDE amendment, filed March 8th. FDA responded on April 6th - per EYEG, FDA noted four deficiencies - which, again, are related to the manufacturing process for OBG. Sterilization of the final product – is also, again, the main subject. EYEG believes that they can sufficiently remedy all of the cited issues within approximately three months and respond to FDA (i.e. file a second IDE amendment) in July – and if all goes well, they hope to have this second PRK pilot study kicked off in Q3. If that timeline proves accurate, it would equate to only ~3 month delay from EYEG's most recent prior expectations. But, given our lack insight into the specifics or scope of the required remediation-related work, we have similar lack of insight into the reasonableness (or not) of the proposed timelines.

SUMMARY DATA

52-Week High	**$2.43**
52-Week Low	**$0.33**
One-Year Return (%)	**-83.37**
Beta	**3.58**
Average Daily Volume (sh)	**494,667**
Shares Outstanding (mil)	**17**
Market Capitalization ($mil)	**$6**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**10**
Insider Ownership (%)	**25**
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 2018 Estimate	**N/A**
P/E using 2019 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)
2017	185 A	148 A	75 A	0 A	408 A
2018	488 E	759 E	1506 E	2173 E	4926 E
2019					9362 E
2020					4884 E

Earnings per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2017	-$0.28 A	-$0.28 A	-$0.24 A	-$0.16 A	-$0.93 A
2018	-$0.23 E	-$0.21 E	-$0.15 E	-$0.12 E	-$0.69 E
2019					-$0.35 E
2020					-$0.32 E

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

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Ph3 EGP-437 Anterior Uveitis Study Completes Enrollment, Topline Data Still Expected in Q3 …

The pace of enrollment of EYEG's EGP-437 anterior uveitis phase III study was slow-going at first but ended strong – including hitting the 75% mark in December (a Valeant-milestone triggering event) and completing enrollment in early April (another Valeant-milestone triggering event). Importantly, management's prior guidance for topline data to be available sometime in Q3 of this year remains intact. As we noted in our March 6th update, assuming topline data is positive, we think this could also represent the next potential inflection point in the share price. If all goes well, it's possible an NDA filing could happen by early next year and move EYEG much closer towards a commercial-stage company.

Per the agreement with Valeant, EYEG is eligible to receive milestone payments of up to $32.5M related to this anterior uveitis indication. Through 2017 (per our calculation) EYEG had received approximately $5.1M (including the $1M upfront payment. While EYEG has not disclosed how the milestones are structured or triggering events, it's possible that major regulatory events – such as NDA filing and FDA approval – could be associated with relatively larger milestone payments. So, continued success in EGP-AU development should provide additional operating capital and help to mitigate (at least to a certain extent) capital-raising dilution (although we do note that EYEG filed in S-1 in March related to the potential issuance of common, convertible preferred and warrants – potentially a harbinger of a near-term raise).

OBG Post-PRK Surgery Program Hits (Another) Snag

EYEG's OBG programs have experienced some ongoing delays as the company continues to work to get IDE approval to commence a second pilot study in (their initial target indication of) post-PRK surgery. As a reminder, in early 2017 EYEG noted that they were aiming to begin a second pilot study in PRK surgery patients sometime in Q2 2017. That was delayed as the company worked to respond to FDA requests including filing an IDE amendment. Per EYEG's explanations in their 10-K (filed March 2nd) and subsequently filed S-1a (April 9th), the bulk of the agency's requests appear to be related to validation of manufacturing process for OBG, including sterilization procedures of the final product.

EYEG addressed FDA's initial requests in an IDE amendment, filed March 8th. FDA responded on April 6th - per EYEG, FDA noted four deficiencies - which, again, are related to the manufacturing process for OBG. Sterilization of the final product – is also, again, the main subject. EYEG believes that they can sufficiently remedy all of the cited issues within approximately three months and respond to FDA (i.e. file a second IDE amendment) in July – and if all goes well, they hope to have this second PRK pilot study kicked off in Q3. If that timeline proves accurate, it would equate to only ~3 month delay from EYEG's most recent prior expectations. But, given our lack insight into the specifics or scope of the required remediation-related work, we have similar lack of insight into the reasonableness (or not) of the proposed timelines.

FDA approval of the PRK IDE is also a gating factor for EYEG to pursue OBG for parallel indications – including punctate epitheliopathies (PE) – a pilot study for which is anticipated to be on-deck (assuming FDA greenlights the PRK clinical program) and will require a separate IDE. Punctate epitheliopathies are symptoms of early epithelial damage which can be caused by a variety of conditions including inflammation, dry eye, viral infection and others – this breadth means the potential U.S. PE-related target market could be relatively huge and in the tens of millions of people (as compared to ~1M market size for PRK). That clearly makes this an attractive indication for label expansion.

As we have note in recent updates, while the delays to OBG clinical programs have been disappointing, we think the de-risked nature of OBG (based on the long history of HA being used in human eyes and its broad use and extensive successful testing for corneal repair in animals) means that the likelihood of eventual commercialization could be reasonably high if positive results of the first PRK pilot study can be confirmed in this proposed follow-on pilot study (although eventual FDA approval would still require a pivotal study). As such, and coupled with the attractiveness and size of the OBG targeted markets (particularly that of PE), we continue to look forward to FDA's action on this IDE.

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 2018
- Receipt of FDA approval/clearance and launch in 2019 or 2020 and receipt of regulatory milestones as well as additional development milestones up until then
- $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 2020, mid-single digit penetration by 2023/2024 and 10% in 2026/2027 (the out-year in our 10-yr DCF model)

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 began in 2017
- Receipt of FDA approval/clearance and launch in 2020 or 2021 and receipt of regulatory milestones as well as additional development milestones up until then
- $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 2020/2021, mid-single digit penetration by 2022/2023 and 15% in 2026/2027

Jade's Pipeline
- 45% probability (revised from previously assumed 50%) of successful FDA approval/clearance of OBG/PRK
- Out-licenses to major ophthalmology-focused company such as Allergan, Novartis or Bausch+Lomb for 20% of net revenues
- U.S. launch in 2019, single digit penetration through 2022/2023
- 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 $3.00/Share
Given the efficacy signals in the cataract surgery phase IIb topline results we are treating the miss on the primary endpoint as a delay (as opposed to failure) to our previously anticipated timeline for eventual commercialization of EGP-437 for post-cataract surgery. While we still incorporate a 70% haircut to revenues to represent risk of regulatory or commercial failure, we have delayed forecasted launch from 2019/2020 to 2020/2021. Despite the delay, as modeled early-years revenue (excluding development milestones) has been rather benign, the change has nominal impact on our DCF-calculated valuation of EYEG.

The stock price has been almost cut in half since the cataract surgery topline data was announced. We think the sell-off is overdone as we do believe that there is still a viable path for an FDA cataract surgery indication. Additionally, the extent of the sell-off suggests the market was valuing cataract surgery at approximately the same as anterior uveitis, OBG and the rest of the company's pipeline, combined – which is wildly divergent with our estimates.

The continued delays to the OBG clinical programs have prompted us to decrease the probability of successful commercialization from 50% to 45%. Depending on which way FDA goes on the pilot study IDE, that could be further revised - either up or down.

While we had not previously assumed a capital raise prior to 2019, we are now incorporating that assumption (and at a lower than previously assumed valuation). 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 $3.00/share (updated from $4.50/share – the majority of the difference relates to change in modeled share count). While our target price 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 $)

	2017 A	Q1E	Q2E	Q3E	Q4E	2018 E	2019 E	2020 E
Milestones & Royalties	$0	$488	$759	$1,506	$2,173	$4,926	$9,362	$4,884
Collaboration Revenue (Jade, Gov't grants)	$408	$0	$0	$0	$0	$0	$0	$0
Total Revenues	$407.5	$487.5	$759.4	$1,505.6	$2,173.1	$4,925.6	$9,361.6	$4,883.9
YOY Growth	-39.1%	164.2%	412.1%	1915.7%	-	1108.7%	90.1%	-47.8%
Cost of Revenues	$0.00	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Gross Income	$407.5	$487.5	$759.4	$1,505.6	$2,173.1	$4,925.6	$9,361.6	$4,883.9
Gross Margin	-	-	-	-	-	-	-	-
R&D	$10,330.3	$3,111.0	$3,244.0	$3,355.0	$3,450.0	$13,160.0	$11,668.0	$7,445.0
% R&D	2534.9%	638.2%	427.2%	222.8%	158.8%	267.2%	124.6%	152.4%
SG&A	$4,636.4	$1,288.0	$1,377.0	$1,488.0	$1,558.0	$5,711.0	$6,958.0	$7,222.0
% SG&A	1137.7%	264.2%	181.3%	98.8%	71.7%	115.9%	74.3%	147.9%
Operating Income	($14,559.2)	($3,911.5)	($3,861.6)	($3,337.4)	($2,834.9)	($13,945.4)	($9,264.4)	($9,783.1)
Operating Margin	-3572.7%	-802.4%	-508.5%	-221.7%	-130.5%	-283.1%	-99.0%	-200.3%
Total, other income (exp)	($0.7)	($0.5)	($1.0)	($1.4)	($1.5)	($4.4)	($7.4)	($8.8)
Pre-Tax Income	($14,559.9)	($3,912.0)	($3,862.6)	($3,338.8)	($2,836.4)	($13,949.8)	($9,271.8)	($9,791.9)
Taxes	($1,342.0)	$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	($13,217.9)	($3,912.0)	($3,862.6)	($3,338.8)	($2,836.4)	($13,949.8)	($9,271.8)	($9,791.9)
YOY Growth	-	-	-	-	-	-	-33.5%	5.6%
Net Margin	-	-	-	-	-	-	-	-
EPS	($0.93)	($0.23)	($0.21)	($0.15)	($0.12)	($0.69)	($0.35)	($0.32)
YOY Growth	-38.6%	-18.6%	-22.6%	-36.9%	-26.2%	-25.5%	-49.3%	-9.7%
Diluted Shares O/S	14,260	17,205	18,100	22,000	23,500	20,201	26,500	31,000

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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[1], 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

[1] 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

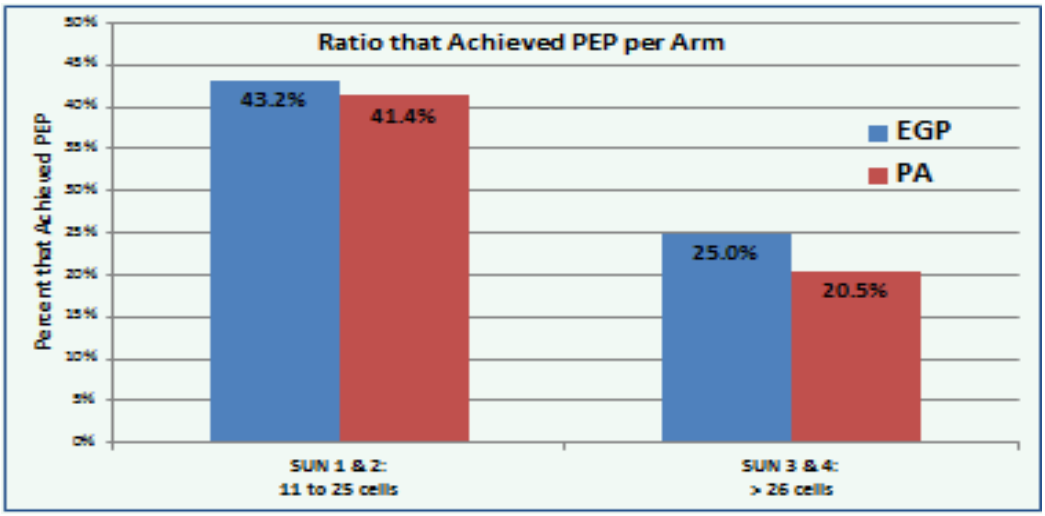
Results: (per information contained in company public filings) While response rates were similar in both the ITT and PP populations, non-inferiority (as pre-defined in the study protocol) was just missed.

- 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;

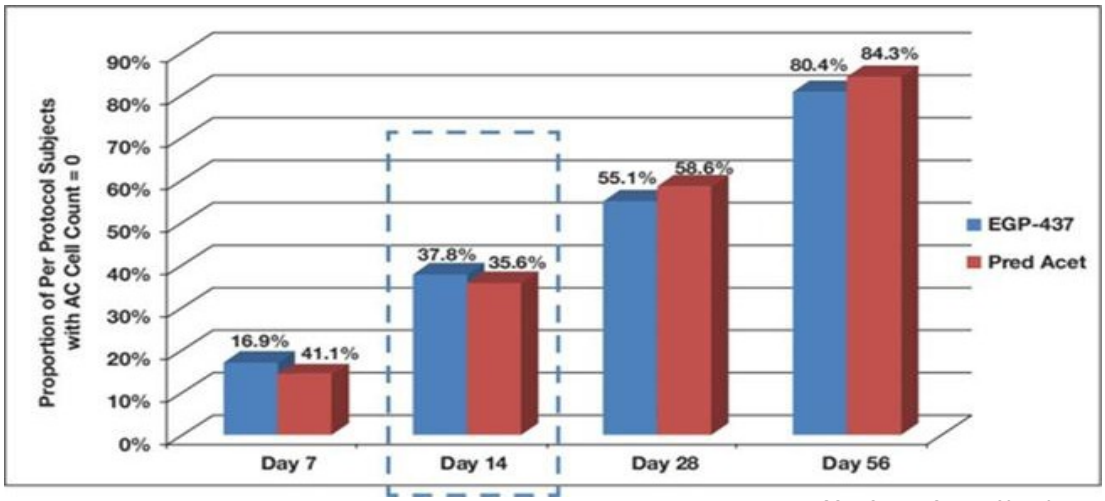
- Greater Proportion of High ACC Count Patients in EGP-437 Arm: a higher proportion of EGP-437 patients (52 of 96, or 54%) had baseline ACC counts greater than 25 as compared to those in the PA arm (40 of 97, or 41%). A post-hoc analysis was done on these high ACC count (i.e. potentially harder to treat)

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

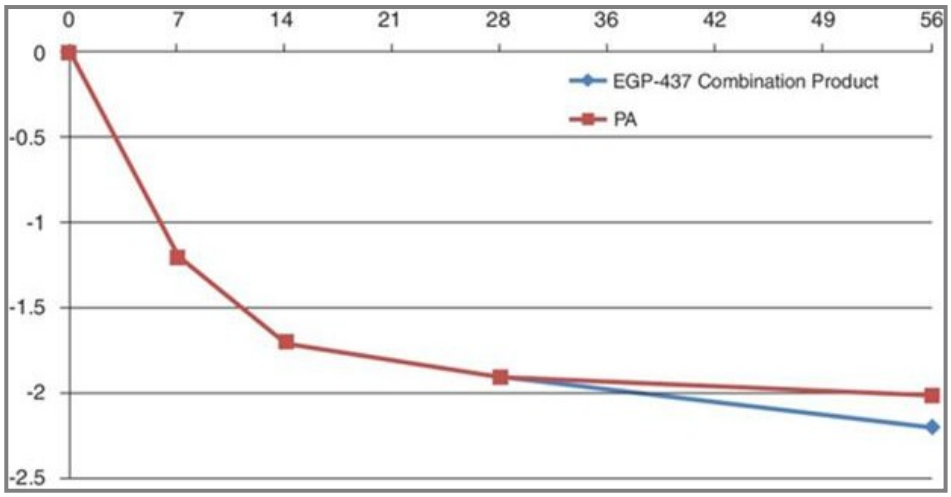
- Similar Complete Response Timeframes: "Time to anterior chamber cell count and score of zero" was a secondary endpoint. Despite the baseline difference in severity of disease (as measured by ACC count), the time to reach ACC count of zero was generally similar in both arms throughout the study (chart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

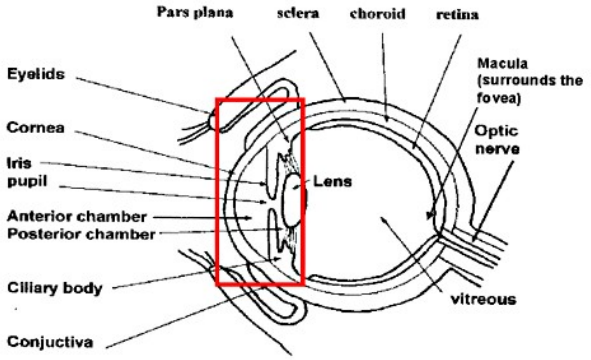
Key Takeaways:

- 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

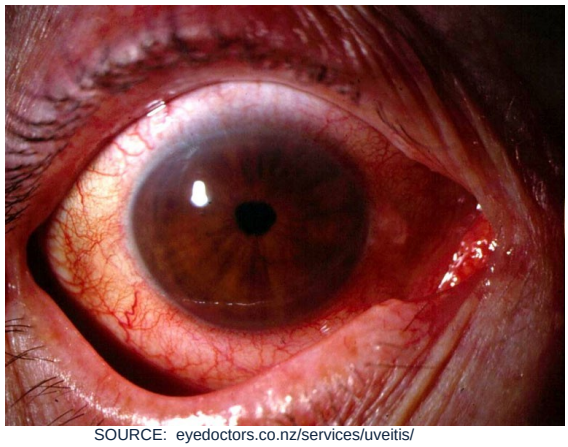
Uveitis is a generic term used to describe inflammation of the uvea. It can occur either in isolation or be the result of an underlying medical condition in other parts of the body. The uvea is the middle layer of the eye, below the white of the eye, and consists of the iris (colored portion), choroid 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[2,3,4,5] - 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,

[2] 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

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

[4] 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

[5] 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.[6]

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.

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

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

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 unprecedented 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.[7] 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;

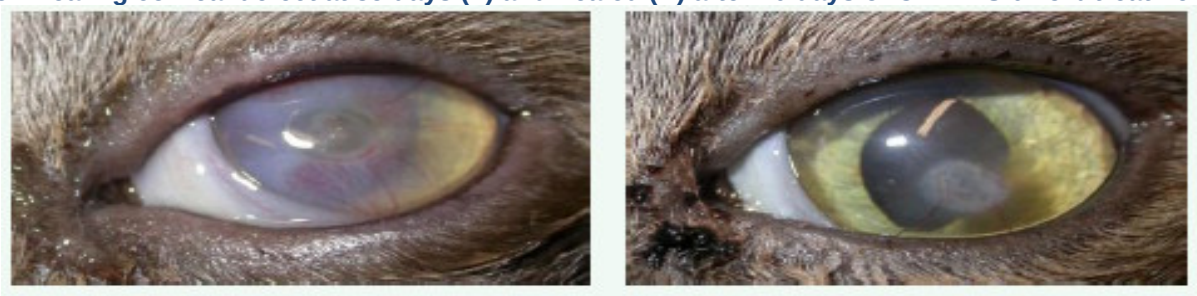
- Persistent corneal epithelial defects (PCED)
- Following photoreactive keratectomy (or PRK, which is similar to LASIK)

[7] 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.

- 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[8]



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



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.

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.

[8] Jade Therapeutics, Eyegate Pharmaceuticals

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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