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Zacks Small-Cap Research

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EyeGate Pharmaceuticals (EYEG-NASDAQ)

EYEG: Focus Is On OBG As U.S. Pilot Studies Fully Enrolled. Data in Q4. EGP-437 Ph3 AE Data Disappoints…

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 $2.50/share.

Current Price (09/28/18)	$0.37
Valuation	**$2.50**

OUTLOOK

The last few months have been somewhat bitter-sweet for EYEG's pipeline. The good news is that both current OBG programs – in PRK and PE – are not only tracking anticipated timelines, but are rapidly moving through their respective human pilot studies with both fully enrolled as of earlier this week. Our hope has been that, given the already-established strong safety profile of hyaluronic acid (as supported by its extensive use for optic care in both pets and humans) and the potential for superior efficacy (or adjunctive/second-line status) to current leading eye therapy compounds (such as cyclosporine and lifitegrast), that OBG could have the makings of a platform-type technology with utility across several ocular hydration and healing commercial categories (including both Rx and non-Rx). Recent IDE approval and subsequent rapid enrollment of both studies has us hopeful that these parallel programs will continue to move swiftly. And, assuming results are positive – and build on the positive data from the initial PRK pilot study data, that could provide more insight into what the potential commercial opportunity might look like (in at least, these initial two target indications). As EYEG is shooting to have top-line data from these pilot studies before the end of this year, our wait may not be long. Disappointing EGP-437 AE Ph3 data means the focus is squarely on OBG.

SUMMARY DATA

52-Week High	**$1.38**
52-Week Low	**$0.29**
One-Year Return (%)	**-69.91**
Beta	**3.46**
Average Daily Volume (sh)	**495,499**
Shares Outstanding (mil)	**43**
Market Capitalization ($mil)	**$16**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**40**
Insider Ownership (%)	**44**
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	1096 A	242 A	186 E	41 E	1565 E
2019					748 E
2020					745 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	-$0.14 A	-$0.07 A	-$0.07 E	-$0.07 E	-$0.31 E
2019					-$0.34 E
2020					-$0.25 E

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

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Q2 Financial Results, Operating Update…

EYEG reported Q2 2018 financial results and provided a business update. As it relates to the financials, Q2 included additional recognition of the milestone payments earned from Valeant. Through Q2, EYEG collected $13.5M from Valeant related to upfront payments and development milestones associated with the development agreements for EGP-437 in anterior uveitis and post-cataract surgery. In terms of how these payments are recognized on EYEG's financial statements, as a reminder an updated FASB standard governing revenue-recognition for contracts with customers resulted in a $9.5M adjustment to EYEG's deferred revenue balance (as of Jan 1, 2018) – this is solely an accounting adjustment with no cash effect.

In terms of operating expenses, R&D expense was $1.8M, down considerably from both Q2'17 ($2.3M) as well as from Q1'18 ($2.5M). The yoy decrease was largely attributed to less spend related the EGP-437 cataract surgery program. The mixed phase IIb results, announced in February of this year, put this program 'under review' by EYEG. Meanwhile, SG&A expense was $1.2M in Q2, flat yoy and up 26% from $954k in Q1. While we had previously expected that operating expenses would trend higher through the end of 2018 and into 2019 based on anticipated ramping of the EGP-437 anterior uveitis (AE) program and CMHA-S/OBG in PRK and PE, the disappointing EGP-437 AE phase III data prompted downward revisions to our forecasted near-term R&D spend. More on this topic below.

Cash: Bolstered by the $10.1M, net ($11.3M gross), raise in April from the sale of 14.7M shares of common stock and 6,536 shares of convertible preferred, as well as from a $1M milestone payment from Valeant (in Q2, related to Ph3 AE study enrollment completion), cash balance was $12.6M at Q2 quarter-end. While were hopeful that topline data of the phase III AE study would be positive and result in another (cash) milestone payment from Valeant, that unfortunately was not the case. Nonetheless, current cash balance provides EYEG with breathing room and should get them to (at least) readout of the two OBG pilot studies – at which point a subsequent raise could be at a better-than-current valuation.

Operational Update: *Both OBG Pilot Studies Moving Fast but Disappointing EGP-437 Ph3 Anterior Uveitis Results…*

The last few months have been somewhat bitter-sweet for EYEG's development programs. The good news is that both current OBG programs – in PRK and PE – are not only tracking anticipated timelines, but are rapidly moving through their respective human pilot studies with both fully enrolled as of earlier this week. Our hope has been that, given the already-established strong safety profile of hyaluronic acid (as supported by its extensive use for optic care in both pets and humans) and the potential for superior efficacy (or adjunctive/second-line status) to current leading eye therapy compounds (such as cyclosporine and lifitegrast), that OBG could have the makings of a platform-type technology with utility across several ocular hydration and healing commercial categories (including both Rx and non-Rx). Recent IDE approval and subsequent rapid enrollment of both studies has us hopeful that these parallel programs will continue to move swiftly. And, assuming results are positive – and build on the positive data from the initial PRK pilot study data (see below), that could provide more insight into what the potential commercial opportunity might look like (in at least, these initial two target indications) for OBG in eye therapy. As EYEG is shooting to have top-line data from these pilot studies before the end of this year, our wait may not be long.

Refresher on the OBG programs

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. The strong safety profile of the compound and expected (relatively streamlined) de novo 510(k) FDA pathway (in November 2016 FDA confirmed de novo 510(k) is an appropriate pathway for OBG to pursue in seeking U.S. regulatory clearance), means the development-to-commercial timeline could be relatively short. See our Appendix for more background on the compound.

As we have noted in recent updates, 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 (results of which were published in the Journal of Cataract & Refractive Surgery in March 2018) can be confirmed in this 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 further updates from these OBG programs.

Initial PRK Pilot Study Results…

Photorefractive keratectomy ("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). In January 2017 EyeGate announced encouraging

top-line results of its first human OBG pilot study in patients that had undergone PRK surgery. 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. The pilot study compared OBG to artificial tears with bandage contact lens (BCL) in patients undergoing bilateral PRK.

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. Specifically, the 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		54.8%	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.

New PE and PRK Pilot Studies…

These new pilot studies will hopefully further validate OBG's effectiveness in speeding healing of corneal wounds and, in the case of PE, reducing symptoms such as moderate dry eye. As of September 24th, both studies were fully enrolled with top-line data expected by year-end.

- **PRK**: designed largely similar to that of the initial PRK study, with some exceptions. The most significant difference is that this new PRK study does not include an OBG+BCL cohort (as the initial study did) but instead incorporates two OBG-alone treatment arms, differentiated by treatment regimen and overall number of administrations. Clearly, the reason for this new PRK pilot study incorporating two OBG-alone cohorts (and not using an OBG+BCL) arm is because of the superior efficacy of the OBG-alone group in the initial study (see results above). One of the OBG-alone cohorts will be dosed at the same regimen as was used in the first study (i.e. QID for 2 weeks), while the other OBG-alone arm will use a slightly more front-end weighted (i.e. 8x/day for 3 days, then QID for 11 days) dosing schedule and include 21% more aggregate administrations (i.e. 68 vs 56). Presumably, the aim of this new pilot study is determine optimal dosing for later-stage studies (assuming success of this second pilot study).

  Control, which consists of artificial tears (AT) 4x/day for two weeks, is similar to the initial study. Also similar to the initial study, will enroll up to 45 patients (initial study had data on n=39) which have undergone bilateral PRK. Primary endpoint (per clinicaltrials.org) which will be assessed via (a masked) designated reading center, is time to complete corneal re-epithelization (i.e. wound healing) as assessed on Day 3 (same as initial study).

(The following is from EYEG's April 2018 investor presentation (while listed on clinicaltrials.org, not all details are included) so it is possible the actual design may be somewhat different);

- Randomized, masked, controlled 2-weeek study in up to 45 subjects undergoing bilateral PRK
- Subjects randomized to one of three cohorts (n=15 per arm);
  - Arm 1: OBG every 2 hrs (8x/day) for 3 days then QID (i.e. 4x/day) for additional 11 days
  - Arm 2: OBG QID for 2 weeks
  - Arm 3: BCL (Acuvue Oasys plano lens) + AT QID for 2 weeks
- Primary efficacy endpoints based on fluorescein staining:
  - Time to corneal re-epithelization and
  - Proportion of subjects with complete corneal re-epithelization of epithelial defect on day 3
  - Evaluated by a masked reading center (Tufts) using digital photography of fluorescein stained slit lamp photos and image analysis

- **PE**: this is our best-guess of the PE study design based in information in EYEG's April and Sept investor presentations. It is possible that the actual design may differ somewhat from what we have here. Given that this study could provide some early support for OBG in a dry eye targeted indication, we will be quite eager for detailed results (hopefully by year-end). PE study will include 30 patients; 15 x 2 arms (OBG or saline). Specific inclusion/exclusion criteria were not disclosed (although will be of interest if and when disclosed). Primary outcome is decrease in fluorescein staining of the cornea from baseline (Day 0) to each of the four visits. Additional details include;
  - 42-Day trial: 2-week wash-out/run-in followed by 4 weeks of two arms
    - Day-14 screening: all subjects stop all topicals and take saline QID OU for 14 days
    - Day-0 randomization: OBG QID for 28 days vs saline QID OU for 28 days
    - Staining completed on Days 7, 14, 21, 28
  - Primary outcome is decrease in fluorescein staining of the cornea from baseline (Day 0) to each visit (Days 7,14,21,28) between the treatment and control arms

The bad news as it relates to EYEG's pipeline was the dismal topline phase III data of EGP-437 in anterior uveitis that was announced earlier this month. It is not only disappointing, it is surprisingly poor given that we believed the prior phase III data was highly suggestive of (non-random) efficacy favoring EGP-437. We don't see value in rehashing the initial data or in comparing those results to that of this new (i.e. second) phase III study – but, for reference, it is in our Appendix.

EGP-437 Phase III top-line data

As a reminder this was expected to serve as a confirmatory study to the prior phase III EGP-437 study in anterior uveitis. If successful (i.e. demonstrate non-inferiority) this confirmatory study data, along with results of the first phase III anterior uveitis study would have been used as the primary support for an NDA filing. That is now not likely to happen.

Design details include…..randomized, double-blind, placebo-controlled and designed to demonstrate non-inferiority of EGP-437 combination therapy to prednisolone acetate ophthalmic suspension (1%). N=251 (~125 each arm) with anterior segment uveitis (ACC count $\geq$ 11) enrolled at approximately 60 U.S. sites. Patients were randomized to EGP-437 combination therapy or prednisolone acetate ophthalmic suspension (1%). Primary efficacy endpoint was 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

The design of this study, while similar to the initial phase III anterior uveitis trial, had some important differences which we thought would 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).

As the top-line data show, it was far from a success. While 42% of EGP-437 patients reached ACC count of 0, that was crushed by the 60% of control patients that did. Even worse, Chi-square shows the difference was statistically significant favoring control. The slide below is from EYEG's September presentation.

Anterior Uveitis Phase 3 Non-Inferiority Trial

Missed Primary Endpoint on Day 15

- Non-inferiority was not demonstrated between EGP-437 and Control (the lower limit of the two-sided 95% confidence interval (CI) for the difference is less than -10%)
- Control group had higher rate of success (ACC count=zero) than the EGP-437
  - The Chi-square test shows significant difference between Control and EGP-437, preferring the Control group

N	Test	EGP-437 Zero	Control Zero	EGP-Control, Two-Sided 95% CI	p-value[1]/ p-value[2]
251 patients	ACC Count	53 (42.4%)	75 (60.3%)	(-30.25%, -5.55%)	0.8951/ 0.0052

This is the third consecutive clinical study of EGP-437 (anterior uveitis initial ph3, cataract surgery ph2, and anterior uveitis confirmatory ph3) which failed to show statistical significance on the primary endpoint. While the first AE phase III study and the CS phase II study data were, in our opinion, compelling enough to justify continuing ahead, this latest data certainly does not seem to support that theme.

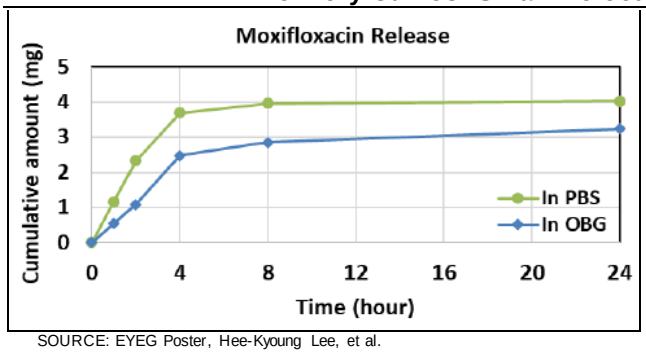
As such, unless the full data set tells a different story or upon further examination investigators find an error in the data or methodology or in how the study was conducted (we are not holding out much hope), we think the chances of a path forward may now be thin for EGP-437. That is, at least as it relates to anterior uveitis – but also perhaps as it relates to the platform. This failure combined with the rapid progress of OBG over the last few months probably means that, at the very least, the pause button is hit on EGP-437 until readout of topline data from the OBG PRK and PE pilot studies.

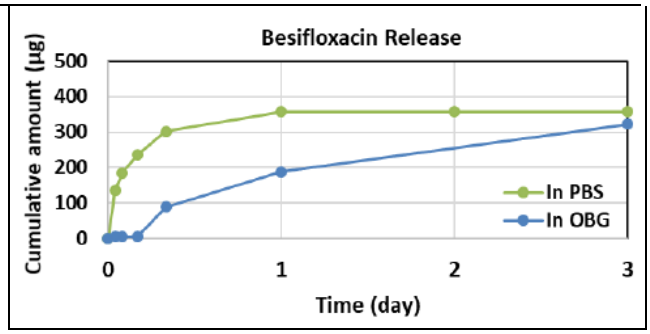
We also think that, assuming continued success in the PRK/PE studies, that CMHA-S programs could reasonably be expanded to include other indications given its safety profile and potential broad applications related to corneal wound healing. Importantly, adding indications could be a fairly streamlined process, and not necessarily require pivotal superiority (to SOC) studies. 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. OBG could have much broader utility, including outside of healing. This is something that we alluded to earlier this year following PoC data for OBG as a delivery vehicle (see below).

OBG Proof-of-Concept in Sustained Delivery of Antibiotics…

OBG could prove to be somewhat of a platform-type technology. Importantly, adding indications could be a fairly streamlined process, and not require pivotal superiority (to SOC) studies. While EYEG's main focus to-date with OBG has been on the healing benefits of hyaluronic acid, initial pre-clinical proof-of-concept indicates that it may have utility as a sustained delivery vehicle for (small molecule) antibiotics. The study showed that a solution containing moxifloxacin and OBG slowed release of the antibiotic as compared to a solution containing moxifloxacin and saline (i.e. standard solution). During the first four hours, 100% of the antibiotics were released from the standard solution while only 60% had been released from the OBG solution. The study also included the antibiotic besifloxacin – both of the release curves (below) for which were similar to those of moxifloxacin.

Delivery Curves: Small Molecule Antibiotics+ OBG vs Saline





SOURCE: EYEG Poster, Hee-Kyoung Lee, et al.

The study also indicated that the addition of antibiotics did not affect either the viscosity or pH values of OBG. Plans for follow-on studies have not yet been announced, although this could lead to a program investigating the ability of OBG to retain antibiotics (such as those used for the treatment of corneal ulcers) on the eyes longer, thereby reducing time (and treatment burden) to healing.

VALUATION

EGP-437 Risk Discount

With the disappointing phase III confirmatory anterior uveitis topline data, our 'risk-of-failure' to reach commercialization discount has substantially increased as it relates to a possible anterior uveitis indication (from 20% to 90%). We have also upwardly adjusted the risk discount for a possible cataract surgery indication (from 70% to 80%).

Punctate Epitheliopathies

Given the relatively huge size of the PE market, we will be eagerly awaiting topline results of the two OBG pilot studies. 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 – perhaps particularly within dry eye. We note that while we began modeling assumed contribution of OBG in PRK following announcement of the positive results of the (initial) pilot study in that proposed indication, we had yet to model any potential future contribution from OBG in any other indication – including for PE.

While we previously believed it prudent to wait for topline data before modeling the PE market, we now think that methodology errs by implying there is no 'value' (or mitigation of failure-risk) associated with progress to-date of these studies (most notably, gaining FDA IDE approval and completing enrollment) and that initial assignable 'value' does not begin until and unless there is positive clinical data. We further support our decision to bring PE into our model given the reasonable likelihood of cross-over efficacy between PRK and PE conditions (i.e. as PRK pilot 1 data was positive, it is reasonable to infer at least some level of efficacy of OBG in PE) and the well-established healing properties (and safety profile) of HA.

PE Market

We expect to refine our assumptions and methodology with continued development progress and success of OBG. As it is now, we are using fairly broad strokes in categorizing the potential OBG-PE target market as we need clinical results to more narrowly define it. For example, we do not know exactly what the pilot study populations look like (inc/exc criteria), how that might compare to a later-stage (pivotal?) study or how efficacy might compare to existing (and other late-stage) therapies. This also means market comp analysis is largely not (yet) reliably useful – including, for example, estimating what portion of Restasis or Xiidra users might benefit from OBG. Certain market-related unknows also introduce risk of forecasting error – for example, timing of Restasis generics in the U.S., numerous potential near-term NDAs/NMEs on the horizon and rampant M&A/licensing activity could influence (good or bad) the PE opportunity. The table below provides some context of what the broader (i.e. level 3) 'dry eye' drug market (90%+ of WW revenue is U.S.) looks like today.

					WW Annual Sales (millions)								Indication Launch In:	
Product	**Company**	**Generic Name**	**Pharmacological Class**	**Indication**	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2024**	**WW**	**US**
Restasis	Allergan	cyclosporine	Tear secretion enhancer	Dry eye	$1,474	$918	$219	$149	$129	$113	$104	$90	4/1/2003	4/1/2003
Refresh	Allergan	carboxymethylcellulose	Eye preparation	Dry eye	$350	$364	$378	$393	$408	$424	$439	$455	12/9/1985	12/9/1985
Xiidra	Shire	lifitegrast	Lymphocyte function-associated	Dry eye	$259	$427	$578	$711	$789	$861	$915	$959	8/29/2016	8/29/2016
Prolacria	Santen	diquafosol tetrasodium	Purinergic receptor P2Y2	Dry eye	$129	$148	$163	$166	$175	$182	$189	$196	12/13/2010	-
Mucosta	Otsuka	rebamipide	Mucin secretagogue	Dry eye	$45	$48	$47	$44	$43	$43	$43	$42	1/5/2012	-
Ikervis	Santen	cyclosporine	Immunosuppressant	Dry eye	$18	$26	$33	$39	$45	$51	$56	$61	7/15/2015	12/31/2021
					$2,275	**$1,930**	**$1,419**	**$1,502**	**$1,590**	**$1,674**	**$1,744**	**$1,803**		

SOURCE: Evaluate Pharma / Zacks Estimates

As we need to start somewhere, we think estimated generic Restasis pricing (i.e. manufacturer to wholesaler after discounts or rebates) of $80 - $150 per monthly Rx is a reasonable input (for context, branded Restasis WAC is currently ~$244). The Rx branded U.S. 'dry eye' market is worth approximately $2.5B, according to our research, with Restasis accounting for approximately 60% of that. Today, ~25M Americans are diagnosed with 'dry eye' but about 3x that many, or 75M, are believed to have symptoms. Exorbitant Restasis pricing had been cited as an impediment to increasing the treated population – which suggests generic Restasis could have the opposite effect. If OBG can be positioned as a second-line (or as an adjunct) therapy for dry eye patients that fail Restasis, generic Restasis (if and when launched) would likely be of significant benefit to OBG uptake.

Our model incorporates the following assumptions:

Anterior Uveitis Indication:

- 10% 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 failure of EGP-437 in the second phase 3 trial, we reduced assumed probability of successful FDA approval/clearance and launch for cataract surgery indication up from 30% to 20%. All modeled milestones and royalties related to cataract surgery are initially discounted by 80% to account for risk of regulatory or commercialization failure
- 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

OBG/PRK

- 50% probability (revised from previously assumed 45%) 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 2019/20, single digit penetration through 2022/2023
- Annual U.S. market for PRK-focused indication of ~$125M

OBG/PE

- 35% probability of successful FDA approval/clearance of OBG/PE

- Out-licenses to major ophthalmology-focused company such as Allergan, Novartis or Bausch+Lomb for 20% of net revenues
- U.S. launch in 2019/2020, single digit penetration through 2022/2023
- Annual U.S. market for PE-focused indication of ~$1.5B

DCF Currently Values EYEG at $2.50/Share

Upward revision to our risk-of-failure discount for EGP-437 in both AE and CS as a result of the latest phase III AE topline data failure has nearly cut our calculated value by a third. However, that is partially offset by an increase in forecasted future cash flow associated with the decision to bring OBG-PE into our model – based on our reasoning explained above. We have also slightly reduced our risk-failure discount to OBG as a whole, which is also based on progress of the pilot studies. As noted, while our OBG-modeling methodology is current generalized, we hope to be able to narrow it with further development progress – success in these two pilot studies would likely be if significant benefit to doing so.

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 $2.50/share. While our target price represents attractive upside to the current share price, our calculated value should appreciate further on progression of OBG through these pilot studies. Upside to our target price could happen if a reasonably viable path forward for EGP-437 is presented. As management and EYEG's advisors have significantly more insight into potential optionality of EGP-437 than we do, we look forward to updates on this as well.

FINANCIAL MODEL

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

	2017 A	Q1A	Q2A	Q3E	Q4E	2018 E	2019 E	2020 E
Valeant Mlstns/Rylts	$0	$1,096	$242	$186	$41	$1,565	$748	$745
Jade, Gov't grants Collab Revenue	$408	$0	$0	$0	$0	$0	$0	$0
Total Revenues	$407.5	$1,096.0	$242.0	$186.0	$41.3	$1,565.3	$747.8	$745.4
YOY Growth	-39.1%	493.9%	63.2%	149.0%	-	284.1%	-52.2%	-0.3%
Cost of Revenues	$0.00	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Gross Income	$407.5	$1,096.0	$242.0	$186.0	$41.3	$1,565.3	$747.8	$745.4
Gross Margin	-	-	-	-	-	-	-	-
R&D	$10,330.3	$2,521.0	$1,837.8	$1,741.6	$1,662.5	$7,762.9	$11,668.0	$7,445.0
% R&D	2534.9%	230.0%	759.4%	936.3%	-	495.9%	1560.4%	998.8%
SG&A	$4,636.4	$954.0	$1,202.5	$1,248.2	$1,277.8	$4,682.6	$6,442.0	$7,087.0
% SG&A	1137.7%	87.0%	496.9%	671.1%	-	299.2%	861.5%	950.8%
Operating Income	($14,559.2)	($2,379.0)	($2,798.3)	($2,803.8)	($2,899.0)	($10,880.2)	($17,362.2)	($13,786.6)
Operating Margin	-3572.7%	-217.1%	-1156.3%	-1507.4%	-7028.0%	-695.1%	-2321.8%	-1849.6%
Total, other income (exp)	($0.7)	($0.3)	$18.1	$13.2	$8.6	$39.6	($7.4)	($8.8)
Pre-Tax Income	($14,559.9)	($2,379.3)	($2,780.3)	($2,790.6)	($2,890.4)	($10,840.6)	($17,369.6)	($13,795.4)
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)	($2,379.3)	($2,780.3)	($2,790.6)	($2,890.4)	($10,840.6)	($17,369.6)	($13,795.4)
YOY Growth	-	-	-	-	-	-	60.2%	-20.6%
Net Margin	-	-	-	-	-	-	-	-
EPS	($0.93)	($0.14)	($0.07)	($0.07)	($0.07)	($0.31)	($0.34)	($0.25)
YOY Growth	-38.6%	-50.5%	-73.1%	-72.8%	-59.6%	-66.8%	10.8%	-26.4%
Diluted Shares O/S	14,260	17,205	37,484	42,555	43,800	35,261	51,000	55,000

Brian Marckx, CFA

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APPENDIX (for background only, may not be current)

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

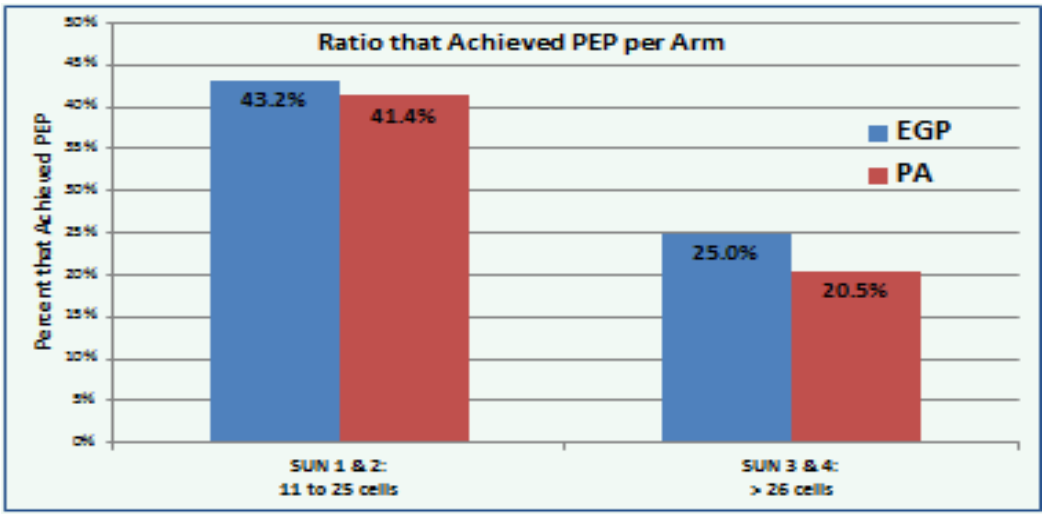
Results: (per information contained in company public filings) While response rates were similar in both the ITT and PP populations, non-inferiority (as pre-defined in the study protocol) was just missed.

- 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;

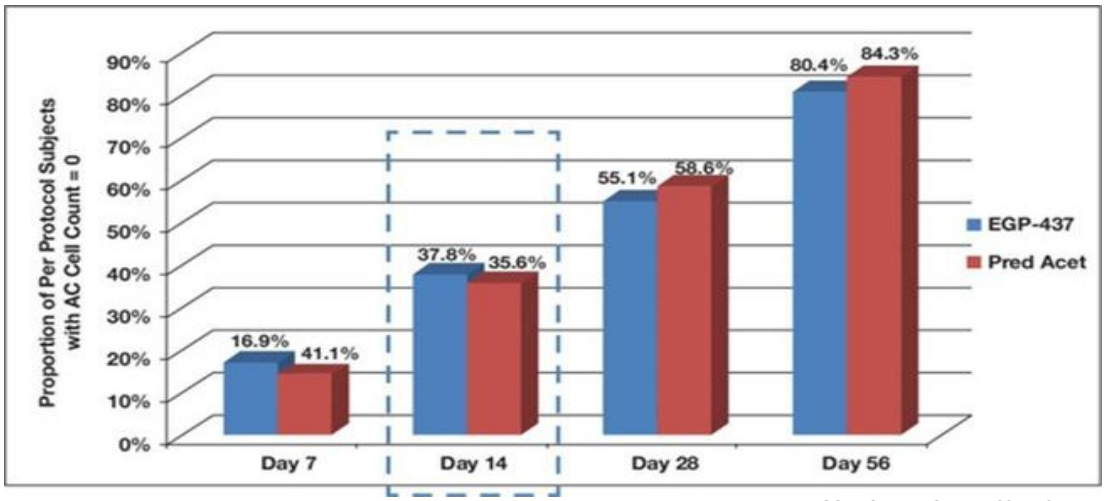
- Greater Proportion of High ACC Count Patients in EGP-437 Arm: a higher proportion of EGP-437 patients (52 of 96, or 54%) had baseline ACC counts greater than 25 as compared to those in the PA arm (40 of 97, or 41%). A post-hoc analysis was done on these high ACC count (i.e. potentially harder to treat)

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

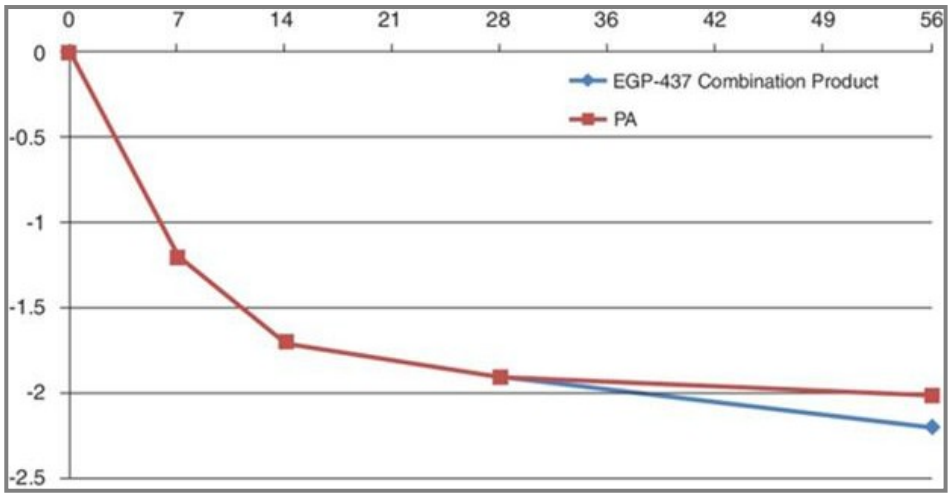
- Similar Complete Response Timeframes: "Time to anterior chamber cell count and score of zero" was a secondary endpoint. Despite the baseline difference in severity of disease (as measured by ACC count), the time to reach ACC count of zero was generally similar in both arms throughout the study (chart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

EGP-437 Anterior Uveitis Phase III Confirmatory top-line data hugely disappointing

As a reminder this was expected to serve as a confirmatory study to the prior phase III EGP-437 study in anterior uveitis. If successful (i.e. demonstrate non-inferiority) this confirmatory study data, along with results of the first phase III anterior uveitis study would have been used as the primary support for an NDA filing. That is now not likely to happen.

Design details include…..randomized, double-blind, placebo-controlled and designed to demonstrate non-inferiority of EGP-437 combination therapy to prednisolone acetate ophthalmic suspension (1%). N=251 (~125 each arm) with anterior segment uveitis (ACC count $\geq$ 11) enrolled at approximately 60 U.S. sites. Patients were randomized to EGP-437 combination therapy or prednisolone acetate ophthalmic suspension (1%). Primary efficacy endpoint was 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

The design of this study, while similar to the initial phase III anterior uveitis trial, had some important differences which we thought would 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).

Topline data were announced in early September 2018. As the top-line data show, it was far from a success. While 42% of EGP-437 patients reached ACC count of 0, that was crushed by the 60% of control patients that did. Even worse, Chi-square shows the difference was statistically significant favoring control. The slide below is from EYEG's September presentation.

Anterior Uveitis Phase 3 Non-Inferiority Trial

Missed Primary Endpoint on Day 15

- Non-inferiority was not demonstrated between EGP-437 and Control (the lower limit of the two-sided 95% confidence interval (CI) for the difference is less than -10%)
- Control group had higher rate of success (ACC count=zero) than the EGP-437
  - The Chi-square test shows significant difference between Control and EGP-437, preferring the Control group

N	Test	EGP-437 Zero	Control Zero	EGP-Control, Two-Sided 95% CI	p-value[1]/ p-value[2]
251 patients	ACC Count	53 (42.4%)	75 (60.3%)	(-30.25%, -5.55%)	0.8951/ 0.0052

This is the third consecutive clinical study of EGP-437 (anterior uveitis initial ph3, cataract surgery ph2, and anterior uveitis confirmatory ph3) which failed to show statistical significance on the primary endpoint. While the first AE phase III study and the CS phase II study data were, in our opinion, compelling enough to justify continuing ahead, this latest data certainly does not seem to support that theme.

As such, unless the full data set tells a different story or upon further examination investigators find an error in the data or methodology or in how the study was conducted (we are not holding out much hope), we think the chances of a path forward may now be thin for EGP-437. That is, at least as it relates to anterior uveitis – but also perhaps as it relates to the platform. This failure combined with the rapid progress of OBG over the last few months probably means that, at the very least, the pause button is hit on EGP-437 until readout of topline data from the OBG PRK and PE pilot studies.

CATARACT SURGERY

As a reminder, Valeant picked up their option for a cataract surgery indication. In February 2017 EYEG announced that in return for $4M upfront cash (received in Q1 2017) 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.

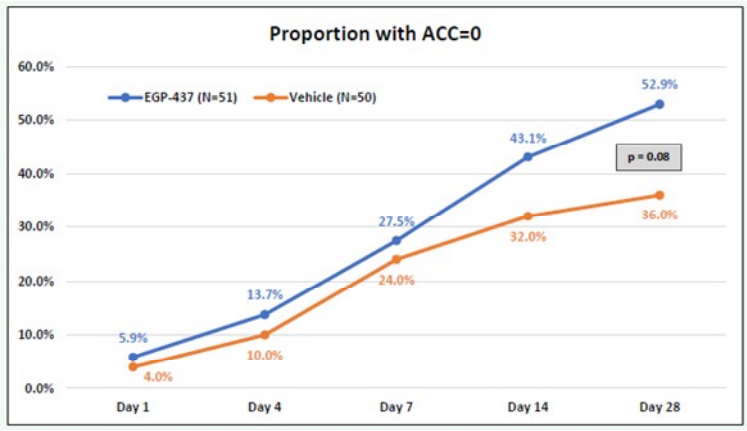
In February 2018 EyeGate announced top-line results of its phase IIb study evaluating the safety and efficacy of EGP-437 in patients which underwent cataract surgery with implantation of a monofocal posterier chamber intra-ocular lens (IOL). Primary efficacy endpoint is the proportion of subjects with an anterior chamber (AC) cell count of zero at Day 7 and the proportion of subjects with pain score of zero at Day 1. Secondary endpoints are change in mean ACC on Day 7 and change in mean pain score on Day 1.

Final enrollment was 106 patients (of which 101 were evaluable) across seven U.S. trial sites. Subjects were randomized immediately after surgery to either EGP-437 (iontophoresis with 40 mg/mL dexamethasone phosphate) (n=51) or placebo (iontophoresis with 100 mM sodium citrate solution) (n=50). Evaluations were completed at Days 0, 1, 4, 7, 14 and 28.

While top-line results showed that the primary endpoints were not met, details within the data indicate that there was a positive treatment effect. We may know more when the full data is analyzed and released. EYEG noted in their February 5th press release that while statistical significance was not reached on the co-primary endpoints, that both secondary measures did show statistical significance (p=0.0096 on mean change in ACC at Day 7 and p=0.0149 on mean change in pain score at Day 1).

In addition, and also supporting the theme of a positive treatment effect of EGP-437, was that a greater percentage of placebo patients required rescue by Day 14 and, unlike EGP-437 patients, rescues continued in the placebo arm between Day 14 and Day 28. And finally, throughout the study and on every evaluation day, a greater proportion of treatment patients had ACC of 0 as compared to placebo patients and this separation continued to grow from Day 7 until the final evaluation on Day 28 (chart below). We think this divergence over time is particularly compelling. EYEG also notes that EGP-437 safety profile was favorable with no SAEs reported.

Efficacy Favors EGP-437 At Every Time Point



SOURCE: EyeGate Feb 2018 Presentation

Our Comments…
While the full data is still being analyzed, based on our discussion with management, it appears that results may have been influenced by a greater than anticipated proportion of patients in the placebo arm having little to no post-surgical inflammation. While speculation, we think it is possible that recent advances in surgical procedures may play a part in lower rates of inflammation. Regardless, just one day after surgery 48% of placebo patients had either no inflammation (i.e. ACC = 0) or mild inflammation (mild inflammation if typically considered to ACC < 10). This included 4% of the placebo group that had no inflammation. Further analysis indicated that had these patients been excluded from the study that there would have been an even greater separation of treatment vs. placebo on the primary endpoint of ACC = 0 at Day 7 – potentially enough to reach statistical significance.

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 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.[2] 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…

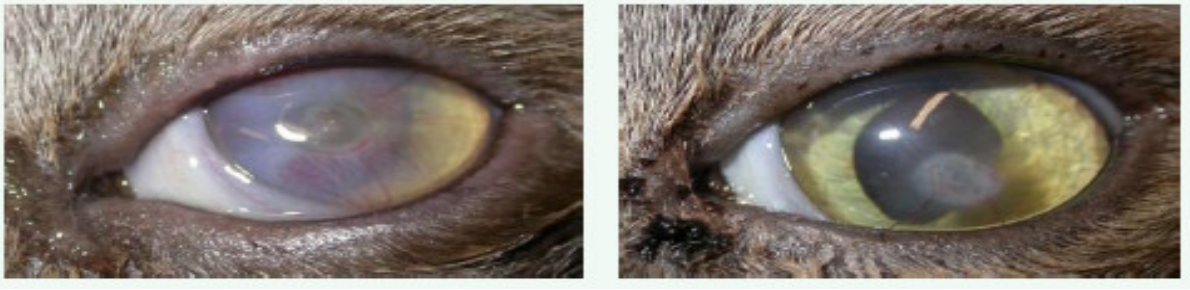
The initial indication EYEG expects to seek is for corneal repair with EyeGate Ocular Bandage Gel', or OBG (initially JDE-003) for populations such as;

- 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.

[2] 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.

Non-healing corneal defect at 35 days (L) and healed (R) after 10 days of CMHA-S 0.75% treatment[3]



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.

[3] Jade Therapeutics, Eyegate Pharmaceuticals

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