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EyeGate Pharmaceuticals (EYEG-NASDAQ)

EYEG Submits IDE to FDA Seeking Approval to Commence Pivotal PRK Study

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 $2.25/share.

Current Price (05/02/19)	$0.28
Valuation	**$2.25**

OUTLOOK

EYEG announced that they submitted an IDE application to the FDA seeking approval to commence a pivotal study for OBG in PRK. FDA turnaround is anticipated in approximately 30 days. EYEG notes that while they wait for the U.S. regulatory agency's answer, they will continue with the initiation of the planned study which, if successful, is expected to be used as primary support for a De Novo filing.

The timing of this IDE filing is commensurate with management's prior guidance (of filing in Q2'19). The company had previously indicated that, based on this anticipated De Novo pathway, that they hope to commence a pivotal study for PRK in Q2, complete it in Q3 and to have regulatory clearance for a PRK indication in 2020.

We look forward to hearing additional details about the planned design of the pivotal PRK study as well as the next steps for development of OBG in PE. As it relates to the planned pivotal study for PRK, we will be particularly interested to know if the study design is single arm (such as was utilized by Allergan with Oculeve / TrueTear) or if includes comparator (which would imply FDA requires non-inferiority or superiority). Based on EYEG's timelines (i.e. to complete the study in Q3), that may suggest this is a single-arm study (which would further bolster our confidence of ultimate success).

SUMMARY DATA

52-Week High	**$0.86**
52-Week Low	**$0.27**
One-Year Return (%)	**-45.01**
Beta	**2.26**
Average Daily Volume (sh)	**222,469**
Shares Outstanding (mil)	**44**
Market Capitalization ($mil)	**$12**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**41**
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 2019 Estimate	**N/A**
P/E using 2020 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**High,**
Type of Stock	**Small-Value**
Industry	**Med-Tech**

ZACKS ESTIMATES

Revenue
(in 000s of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2018	1096 A	242 A	315 A	0 A	1653 A
2019	0 E	0 E	0 E	0 E	0 E
2020					65 E
2021					7659 E

Earnings per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2018	-$0.14 A	-$0.07 A	-$0.07 A	-$0.06 A	-$0.30 A
2019	-$0.05 E	-$0.06 E	-$0.06 E	-$0.06 E	-$0.23 E
2020					-$0.23 E
2021					-$0.14 E

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

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WHAT'S NEW…

EYEG Submits IDE to FDA Seeking Approval to Commence Pivotal PRK Study
This morning EYEG announced that they submitted an Investigational Device Exemption (IDE) application to the FDA seeking approval to commence a pivotal study for OBG in PRK. FDA turnaround is anticipated in approximately 30 days. EYEG notes that while they wait for the U.S. regulatory agency's answer, they will continue with the initiation of the planned study which, if successful, is expected to be used as primary support for a De Novo filing.

The timing of this IDE filing is commensurate with management's prior guidance (of filing in Q2'19). The company had previously indicated that, based on this anticipated De Novo pathway, that they hope to commence a pivotal study for PRK in Q2, complete it in Q3 and to have regulatory clearance for a PRK indication in 2020.

Next steps and could PE follow in short-order?...
We look forward to hearing additional details about the planned design of the pivotal PRK study as well as the next steps for development of OBG in PE. As it relates to the planned pivotal study for PRK, we will be particularly interested to know if the study design is single arm (such as was utilized by Allergan with Oculeve / TrueTear) or if includes comparator (which would imply FDA requires non-inferiority or superiority). Based on EYEG's timelines (i.e. to complete the study in Q3), that may suggest this is a single-arm study (which would further bolster our confidence of ultimate success).

As it relates to PE, we wonder if this could represent a relatively simple label expansion if and when OBG successfully navigates the De Novo pathway for PRK. More specifically, could a PE indication be added with successful completion of a relatively small, single-arm study demonstrating improvement in dry eye symptoms based on SPEED or OSDI (similar to how TrueTear secured its severe dry eye indication)? If so, and EYEG is able to meet their anticipated 2020 timeline for FDA clearance for PRK, it is conceivable that a PE indication could follow in short-order.

We also think that, assuming continued success in the PRK/PE programs, that CMHA-S 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 in 2018 following PoC data for OBG as a delivery vehicle.

(See below for a refresher on both the OBG PRK and PR programs)

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) are confirmed in this follow-on pilot study. While the topline data suggests that may have been the case – we'll reserve final judgment when the totality of the data is available. And while we had previously believed that FDA clearance would still eventually require larger 'pivotal' studies (i.e. demonstrating superior efficacy to standard of care), more recent additional due diligence on the FDA pathways of like-kind therapies (specifically that of Oculeve, Inc's Intranasal Tear Neurostimulator and Allergan's TrueTear) suggest to us that that may not necessarily be the case.

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 indicated 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.

Initial PE and 2nd PRK Pilot Studies…

Results of these most recent pilot studies, announced in mid-November 2018, appear to further support the effectiveness of OBG in healing of corneal wounds (PRK) and in the treatment of dry eye (PE).

2nd PRK Pilot study design: Officially titled, *A Randomized, Masked (Reading Center), Prospective Pilot Study of the Safety and Effectiveness of the EyeGate Ocular Bandage Gel, a 0.75% Crosslinked Hyaluronic Acid Applied Topically, Versus a Bandage Contact Lens for Acceleration of Re-epithelialization of Large Corneal Epithelial Defects in Patients Having Undergone Photorefractive Keratectomy (PRK),* it was designed largely similar to that of the initial PRK study, with some exceptions. The most significant difference is that this second PRK study did not include an OBG+BCL cohort (as the initial study did) but instead incorporated 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 was because of the superior efficacy of the OBG-alone group in the initial study.

One of the OBG-alone cohorts was dosed at the same regimen as was used in the first study (i.e. QID for 2 weeks), while the other OBG-alone arm used a slightly more front-end weighted (i.e. 8x/day for 3 days, then QID for 11 days) dosing schedule and included 21% more aggregate administrations (i.e. 68 vs 56). While we had presumed

that the aim of this second pilot study was to determine optimal dosing for later-stage studies (assuming success), we now believe that it might be possible that follow-on studies may not be required for support of an FDA filing.

The study enrolled 45 patients (initial study n=39) which had undergone bilateral PRK (with epithelial removal using alcohol in a 9.0 mm well or trephine at the time of surgery to ensure consistency of the size of the ablation area). Control, which consisted of artificial tears (AT) 4x/day for two weeks, is similar to the initial study. **Primary endpoint (per clinicaltrials.org) which was assessed via (a masked) designated reading center (Tufts), was time to complete corneal re-epithelization (i.e. wound healing) as assessed on Day 3 (same as initial study) post-surgery.** (The following is from EYEG's public filings, PRs and presentations (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-week 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

Results: Topline results were announced in a press release on November 13th and reported on epithelial healing as of Days 2, 3 and 4 (post-surgery). We note that while the clinicaltrials.org study design description does not reference Day 2 or Day 4 endpoints, we think they may have been included as a secondaries. As it relates to endpoints, EYEG's 2018 10-K states that efficacy assessments included wound healing on Days 3 and 4 and wound size on Day 3. Below we include the totality of the results that EYEG released, which was sourced from PRs, SEC filings and investor presentations.

- Day 3: on the **primary endpoint of complete** corneal re-epithelization (i.e. wound healing), 73% (11/15) of Arm 1 OBG and 87% (13/15) of Arm 2 OBG eyes were completely healed (i.e. met the primary endpoint), compared to just 67% (10/15) of eyes receiving standard of care (SOC)
- Day 4: 100% (15/15) of eyes treated with both OBG regimens were completely healed at Day 4, compared to 87% (13/15) of eyes treated with SOC

PRK Study 2: rate of healing favors both OBG arms versus control

	Number of Healed Eyes using OBG vs. Standard of Care				Ocular Bandage Gel: % Better and Standard of Care		
	Group 1 (N = 15)	Group 2 (N = 15)	Control Group (N = 15)		Group 1 (N = 15)	Group 2 (N = 15)	Control Group (N = 15)
Day 3	11	13	10	Day 3	73.3%	86.7%	66.7%
Day 4	15	15	13	Day 4	100.0%	100.0%	86.7%

Source: EYEG Q1'19 Investor Presentation

- Day 2:
  - **maximum wound size** was 67% smaller among Arm 1 OBG and 49% smaller among Arm 2 OBG at Day 2 as compared to SOC
  - **average wound size** was 26% smaller among Arm 1 OBG and 6% smaller among Arm 2 OBG at Day 2 as compared to SOC

PRK Study 2: reduction in wound size favors both OBG arms versus control

Average Wound Size (mm^2)	Group 1 (N = 15)	Group 2 (N = 15)	Control Group (N = 15)
Day 2	3.07	3.91	4.15
Day 3	0.10	0.19	0.16
Day 4	0.00	0.00	0.33
Day 14	0.00	0.00	0.00

Maximum Wound Size (mm^2)	Group 1 (N = 15)	Group 2 (N = 15)	Control Group (N = 15)
Day 2	7.97	12.20	23.95
Day 3	0.99	1.98	1.91

Source: EYEG Q1'19 Investor Presentation

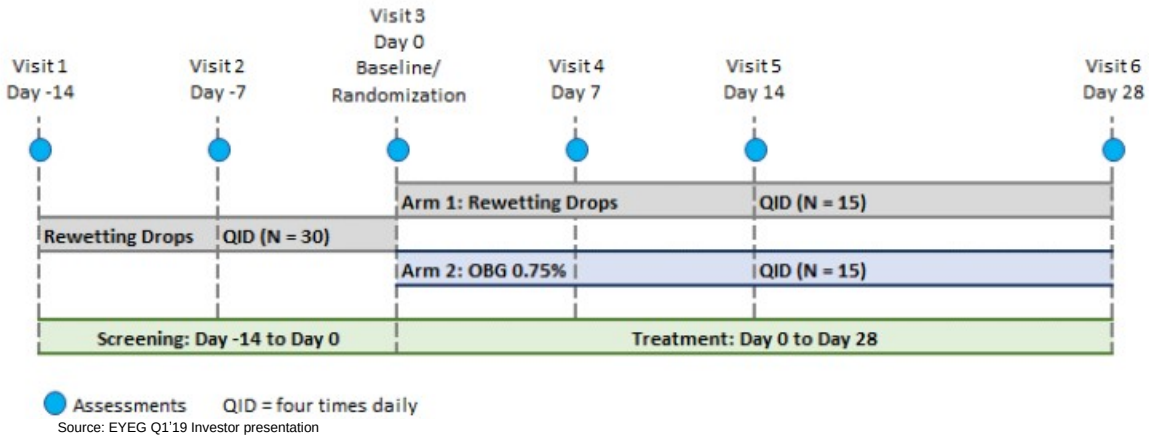
- Safety: "**no concerns**", per topline results announced in November 2018
  - Additional specifics are included in EYEG's Q1'19 investor presentation including
    - Three ocular adverse events in 3 patients; all mild, unrelated, expected and resolved
      - Arm 1 OBG: 1 patient with mild corneal haze at Day 14
      - Control arm: 2 patients with recurrent epithelial erosions all resolved by Day 14
    - No non-ocular adverse events
    - No change in IOP
    - Slight decrease in BCVA on Day 14 in Arm 1 OBG due to mild expected post-PRK corneal haze
    - SPEED used as safety: no worsening of symptoms in either arm. All arms equal at Day 14

OBG PE

The following is our best understanding of the punctate epitheliopathies (PE) study design based on information in EYEG recent investor presentations, press releases and SEC filings. Study included 30 patients; 15 x 2 arms (OBG or B&L rewetting drops) with PEs such as dry eye. Patients with a corneal staining score of NEI $\geq$ 4 were included in the study. Other inclusion/exclusion criteria were not disclosed (although will be of interest if and when disclosed). **Primary outcome** was decrease in fluorescein staining of the cornea from baseline (Day 0) to each of three visits; Days 7, 14 and 28. Results also included **performance on a 'symptomology' assessment**. Symptomology was assessed (at all three visits) using 'standard patient evaluation of eye dryness' (SPEED). SPEED is a well-validated patient reported outcome questionnaire that is designed to evaluate the severity of dry eye symptoms over a certain time period. Symptoms include 'dryness', 'grittiness', 'scratchiness', 'irritation', 'burning', 'watering', 'soreness' and 'eye fatigue' and asks if these are 'problematic', 'tolerable', 'uncomfortable', 'bothersome' or 'intolerable'. SPEED provides a score between 0 and 28, the higher the score, the more severe and intolerable. Additional details of the study design include;

- 42-Day trial: 2-week wash-out/run-in followed by 4 weeks treatment (OBG or saline)
  - 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, 28
- Primary outcome is decrease in NEI fluorescein staining of the cornea from baseline (Day 0) to each visit (Days 7,14, 28) between the treatment and control arms

PE Study Design (results announced Nov 2018)

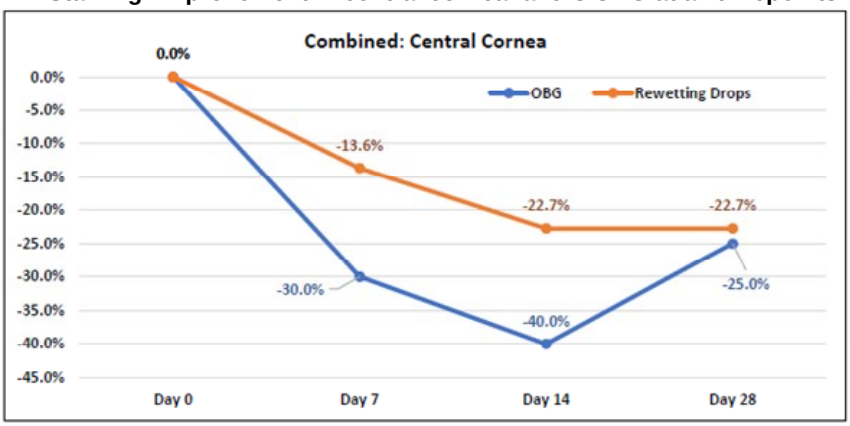


Source: EYEG Q1'19 Investor presentation

Results:

- Staining: while the specifics of results on staining at each of the three visits was not disclosed, we do know that;
  - measurements of the total cornea (which we assume refers to total NEI fluorescein staining score, i.e. primary outcome) did not show a significant difference in reduction between OBG and control treated eyes with OBG achieving 26% reduction and control achieving 23% reduction at Day 7
  - measurements of the central cornea (which we think may be referring to the 'center zone' of the five NEI fluorescein staining zones) showed a reduction of up to 40% for OBG versus up to 23% for control when combining the results of both eyes (the visit Day/time-period was not disclosed)

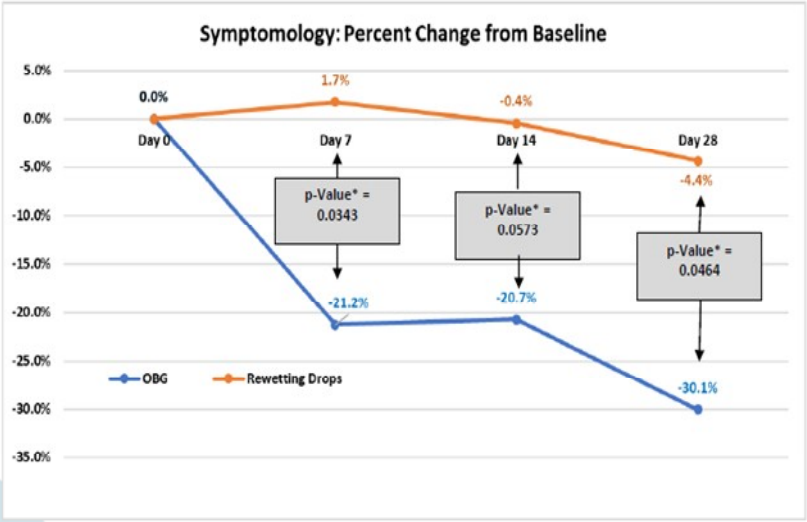
PE Staining: Improvement in central cornea favors OBG at all timepoints



- Symptomology (SPEED)
  - Day 7: statistically significant improvement (p=0.343) favoring OBG
    - OBG arm: SPEED score fell (i.e. symptoms improved) by 21.2% (from 12.9 at baseline to 10.1)
    - Saline: SPEED score increased (i.e. symptoms worsened) by 1.7% (from 15.3 at baseline to 15.5)
  - Day 14: just missed statistical significance (p=0.0573)
    - OBG arm: SPEED score fell (i.e. symptoms improved) by 20.7% (from 12.9 at baseline to 10.2) at Day14)
    - Saline: SPEED score fell (i.e. symptoms improved) by 0.4% (from 15.3 at baseline to 15.2)
  - Day 28: statistically significant improvement (p=0.0464) favoring OBG
    - OBG arm: SPEED score fell (i.e. symptoms improved) by 30.1% (from 12.9 at baseline to 9.0)
    - Saline: SPEED score fell (i.e. symptoms improved) by 4.4% (from 15.3 at baseline to 14.6)
- Safety: "no safety concerns", per topline results announced in November 2018
  - Additional specifics are included in EYEG's Q1'19 investor presentation including
    - One ocular adverse event in the saline arm: mild, unrelated and resolved
      - No ocular adverse events in OBG

- Three non-ocular adverse events in 2 patients in OBG arm and one in 1 saline arm patient
  - All mild unrelated and resolved (hepatic stenosis, strep infections, H. pylori, etc)
- No change in slit lamp exam, IOP or BCVA
- SPEED was used as safety: no worsening of symptoms in OBG

SPEED Symptomology Significantly Different Favoring OBG



SPEED Questionnaire		
Max score = 28		
	Mean Score	
	OBG	Saline
Day -14	14.3	16.8
Day 0	12.9	15.3
Day 7	10.1	15.5
Day 14	10.2	15.2
Day 28	9.0	14.6
Change from Day 0	(3.9)	(0.7)
	Median Score	
	OBG	Saline
Day -14	15.0	16.0
Day 0	15.0	17.0
Day 7	9.0	17.0
Day 14	9.0	17.0
Day 28	8.0	15.0

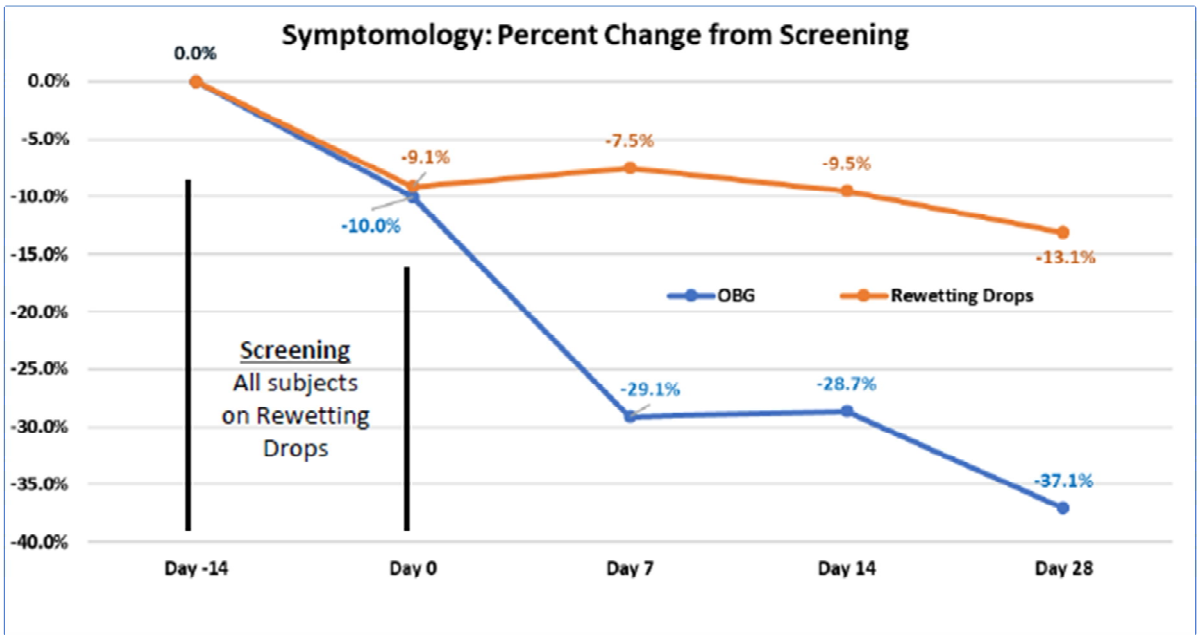
Source: EYEG Q1'19 Investor Presentation

Separation even more evident when evaluated prior to 14-day washout…

The investigators also evaluated the change in SPEED scores (i.e. dry eye symptoms) from initial screening, that is, prior to the 14-day washout, through Day 0 (randomization day) and each evaluation period; Days 7, 14 and 28. What they found was that the OBG subjects showed even greater improvement in dry eye symptoms as compared to those in the saline (rewetting drops) when using the initial screening visit as a proxy for 'baseline'. The results (below, and see table above) suggest that;

- saline improved symptoms of both cohorts similarly during the 14-day washout
- there was immediate separation favoring OBG once the treatment phase began

Symptomology Improvement Favoring OBG Even More Evident Prior to 14-Day Washout



Source: EYEG Q1'19 Investor Presentation

Our comments
The PE and both PRK studies were relatively small and not necessarily fully powered for statistically significance. As such, we cannot make any concrete conclusions regarding efficacy of OBG versus standard of care for either potential indications. Despite that, we think the data does suggest an efficacy signal is present and safety has been a complete non-issue.

As it relates to PRK, this second pilot study data supports the findings in the initial study, specifically that OBG may be associated with more rapid healing than standard of care. And as it relates to PE the SPEED (i.e. reduction in symptoms) scores at two (Days 7 and 28) of the three (Days 7, 14, 28) were statistically superior favoring OBG and Day 14 just barely missed (p=0.0573) statistical significance (also favoring OBG). And, while the (disclosed) NEI staining results were not statistically different between OBG and control, there was a numerical difference supporting the former at Day 7 on the total cornea. And, again, these were relatively small studies and not expected to be powered for efficacy. In addition, the efficacy signal appears to have been even more pronounced in the central cornea – the area of the eye most susceptible to inflammatory response and permeated with nerve endings. NEI staining results of the central cornea favored OBG at every time point. So, efficacy in this part of the eye is arguably more important than the other regions or of the total NEI score. In fact, NEI total score has been criticized as it rates all (five) regions of the cornea as equivalent (in determining presence or severity of dry eye), despite certain regions (namely the central cornea) conveying more information about the underlying disease[1].

While we had previously hoped that, given what we think is compelling results (in efficacy and safety) and coupled with precedent of FDA granting De Novo classification for a dry eye medical device without support from an RCT/pivotal study, that EYEG might be able to follow a similar pathway. Specifically, we had hoped that a pivotal study would not be required and that the existing PRK / PE data would suffice to support an application seeking De Novo classification. Based on the fact that EYEG made an IDE filing (per May 2, 2019 PR) seeking approval to commence a pivotal study for PRK, it is clear that at least one more study will be required.

Precedent indicates FDA does not require superiority to SOC or clinically meaningful outcomes-based endpoints for regulatory clearance…
FDA clearance has been achieved for devices for the treatment dry eye which did not require demonstrating superiority (or non-inferiority) against standard of care. An example is Allergan's (Oculeve, Inc's at the time) Intranasal Tear Neurostimulator, for which they received FDA marketing approval via De Novo classification request (Class II) in April 2017 which is indicated for "a temporary increase in tear production during neurostimulation in adult patients." Allergan subsequently received FDA marketing approval (May 2018) following successful De Novo classification as a Class II device for an upgraded device called TrueTear, which added Bluetooth connectivity and expanded the label to **"a temporary increase in tear production during neurostimulation to improve dry eye symptoms in adult patients with severe dry eye symptoms".**

These two devices, which are identical other than the mobile connectivity of TrueTear, are fairly simple. When inserted into the nose, they produce a low-level electrical signal which makes the eyes water. They were both cleared by FDA with support from two 'pivotal studies' (OCUN-009 and OCUN-010) which were deemed appropriate to demonstrate the ability of the device to increase tear production. While these studies were used to evaluate the safety and effectiveness of the devices, neither included a dedicated comparator or control arm and, in the case of the legacy device, primary outcomes were not actually clinically outcome-based. Instead each patient acted as both treatment and control and the primary outcome measure was simply whether the device produced tears (the expanded label, as we explain below, did require outcomes-based evidence, although did not require superiority vs control). This, we believe, is essentially analogous to demonstrating that (a hypothetical) device which delivers re-wetting saline drops to the eye, increases the amount of liquid saline on the eye (with sufficient safety).

Allergan's TrueTear Dry Eye Device



Source: Allergan, FDA Medical Device database

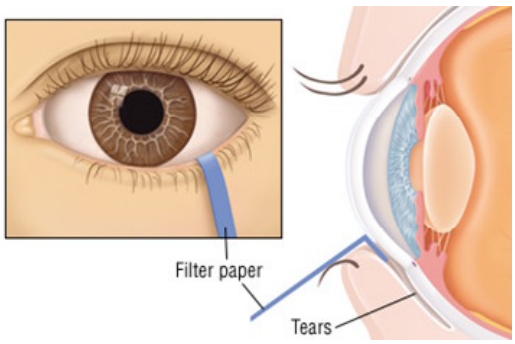
FDA clearance was not predicated on demonstrating superiority to standard of care (or any other comparator). Additionally, the primary endpoint in both of these studies (detailed below) only assesses wetness of the eye immediately following administration but provides no insight into duration of effect. This, we think, is an important point particularly in the context of what is believed to be the unique benefits of EYEG's Ocular Bandage Gel (OBG) – that is, it's gelatin-like properties allow it to remain on the eye longer than liquid drops which is believed to result in

[1] Abelson M. et al. How Do You Quantify The Qualitative? Review of Ophthalmology. August 2016

a longer duration of effect (see sustained delivery curves for use with antibiotics, below, as an example of OBG's relatively long duration of effect).

OCUN-009: 48 patients over two days; Day 1: eligibility assessed, Day 2: the only treatment day. Three arms including two control arms; control 1: device used "off-target" (i.e. outside of the nose), control 2: sham device. On Day 2 each patient received three applications; active treatment, control 1, and control 2. Primary effectiveness outcome was the difference between stimulated (i.e. active treatment) and unstimulated tear production using Schirmer scores). Schirmer test is a very simple validated objective endpoint in which a physician places a small sliver of paper inside the lower eyelid for approximately five minutes. The amount of liquid indicates relative volume of tear production.

Schirmer Test



Source: efei.com

Results showed significantly greater average tear production following stimulated applications; stimulated vs sham ($p<0.0001$) and stimulated vs extra-nasal ($p<0.0001$). In terms of safety, no device-related serious adverse events were reported.

OCUN-010: single-arm, open-label, three-site trial with 97 patients with tear-deficient dry eye evaluated after 180 days of use with Oculeve's device. Patients used the device daily at-home for 180 days and were evaluated with Schirmer test on Days 7, 30, 90 and 180. At each visit, the Schirmer test was first done without stimulation and then done after stimulation – as such, each patient acted as their own treatment and control arm (similar to OCUN-009). Primary efficacy endpoint was the increase in tear production at Day 180 when stimulated versus unstimulated. Secondary endpoints were Schirmer values at Days 0, 7, 30 and 90.

Results showed a significant difference between mean Schirmer scores of the treatment versus control arms at all timepoints. However, there was also a trend towards decreasing tear production with stimulation throughout the 180-assessment period. And, as we noted above and similar to OCUN-009, the study did not include any assessment of dry eye symptoms. In terms of safety, similar to OCUN-009, no device-related serious adverse events were reported.

FDA's approval summary of Oculeve notes that "The two pivotal studies were found to be appropriate to support the action of the device effect (increased tear production during neurostimulation); however, therapeutic benefit, e.g., symptomatic relief from dry eye, was not assessed in the clinical studies."

"Improvement in dry eye symptoms" based on OSDI results…

The label expansion for TrueTear, to include the improvement of dry eye symptoms in people with severe dry eye disease, was approved by FDA based on additional information from the OCUN-010 study. Specifically, the 97 patients in OCUN-010 were evaluated for improvement in dry eye symptoms based on the Ocular Surface Disease Index (OSDI). Symptoms were assessed on Days 0, 7 and 30. This study subset, again was not designed with a comparator arm.

Of the 97 enrolled patients, 77 had dry eye (and therefore were included in the study results). Of these, at Day 30 approximately 25% - 39% had a clinically meaningful improvement[2] while 7% - 12% had a clinically meaningful worsening of their symptoms as compared to baseline.

Cohort	MCID**	Change	Day 7	Day 30
Severe Dry Eye Subgroup	7.3	Improved	42.86% (33/77)	38.67% (29/75)
		Worsened	12.99% (10/77)	12.00% (9/75)
	13.4	Improved	23.38% (18/77)	25.33% (19/75)
		Worsened	5.19% (4/77)	6.67% (5/75)

*OSDI – Ocular Surface Disease Index

**MCID – Minimal Clinically Important Difference

Source: FDA Summary DEN170086

[2] Minimal clinically important difference (MCID) based on those characterized by Miller et al, Arch Ophthalmol 2010;128(1):94-101)

EYEG Anticipates Imminent IND Filing for OBG-PRK Pivotal Study
As a reminder, in November 2016 EYEG announced that, following a pre-submission meeting with FDA, the agency confirmed De Novo was an appropriate pathway for OBG to pursue in seeking U.S. regulatory clearance. Then, more recently in late-March 2019, EYEG announced that FDA "confirmed its path to a de novo filing" and that "FDA has agreed that based on the strength of data from the photorefractive keratectomy ("PRK") pilot study, EyeGate is ready to move forward with a pivotal study, which will allow for a de novo filing."

Given the experience of TrueTear, which did not require a pivotal/comparator/RCT study in securing De Novo Class II classification (and marketing clearance), we were hopeful that OBG could successfully secure De Novo classification with just the existing clinical data. However, the March 2019 press release indicates that, at least as it relates to a PRK-related indication, a pivotal study will be required.

On May 2, 2019 EYEG announced that they submitted an IDE application to the FDA seeking approval to commence a pivotal study for OBG in PRK. FDA turnaround is anticipated in approximately 30 days. EYEG notes that while they wait for the U.S. regulatory agency's answer, they will continue with the initiation of the planned study which, if successful, is expected to be used as primary support for a De Novo filing.

The timing of this IDE filing is commensurate with management's prior guidance (of filing in Q2'19). The company had previously indicated that, based on this anticipated De Novo pathway, that they hope to commence a pivotal study for PRK in Q2, complete it in Q3 and to have regulatory clearance for a PRK indication in 2020.

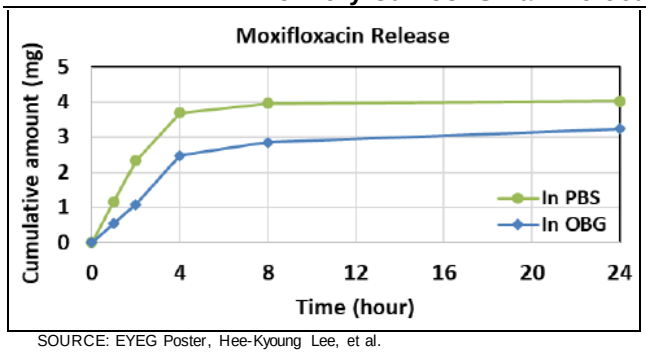
Next steps and could PE follow in short-order?...
We look forward to hearing additional details about the planned design of the pivotal PRK study as well as the next steps for development of OBG in PE. As it relates to the planned pivotal study for PRK, we will be particularly interested to know if the study design is single arm (such as was utilized by Allergan with Oculeve / TrueTear) or if includes comparator (which would imply FDA requires non-inferiority or superiority). Based on EYEG's timelines (i.e. to complete the study in Q3), that may suggest this is a single-arm study (which would further bolster our confidence of ultimate success).

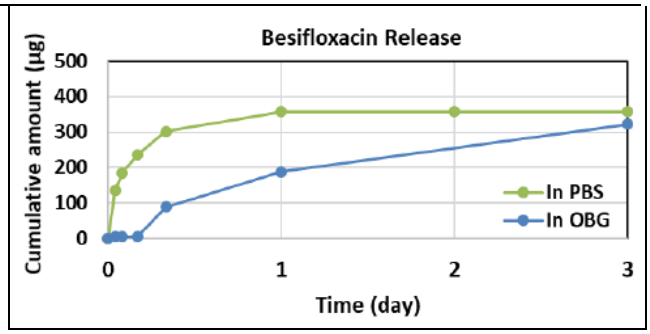
As it relates to PE, we wonder if this could represent a relatively simple label expansion if and when OBG successfully navigates the De Novo pathway for PRK. More specifically, could a PE indication be added with successful completion of a relatively small, single-arm study demonstrating improvement in dry eye symptoms based on SPEED or OSDI (similar to how TrueTear secured its severe dry eye indication)? If so, and EYEG is able to meet their anticipated 2020 timeline for FDA clearance for PRK, it is conceivable that a PE indication could follow in short-order.

We also think that, assuming continued success in the PRK/PE programs, that CMHA-S 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 in 2018 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

Punctate Epitheliopathies

Given the relatively huge size of the PE market, we will be eagerly awaiting next-steps from EYEG of their two OBG programs. 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.

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 study populations look like (inc/exc criteria), how that might compare to a larger population set 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:

OBG/PRK
- 50% probability 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 late-2020, low 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 2021, low single-digit penetration through 2022/2023
    - This includes 1% penetration in 2021 – which represents the vast majority of our modeled $7.7M of net revenue in that year
- Annual U.S. market for PE-focused indication of ~$1.5B

DCF Currently Values EYEG at $2.25/Share

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 $2.25/share. While our target price represents attractive upside to the current share price, our calculated value should appreciate with further development/regulatory progress of OBG. Upside to our target price could happen if a reasonably viable path forward for (or optionality with) EGP-437 is presented.

FINANCIAL MODEL

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

	2018 A	Q1E	Q2E	Q3E	Q4E	2019 E	2020 E	2021 E
Valeant Mlstns/Rylts	$1,653	$0	$0	$0	$0	$0	$0	$0
Jade, Gov't grants Collab Revenue	$0	$0	$0	$0	$0	$0	$0	$0
OBG revenues	$0	$0	$0	$0	$0	$0	$65	$7,659
Total Revenues	$1,652.5	$0.0	$0.0	$0.0	$0.0	$0.0	$64.5	$7,659.2
YOY Growth	305.5%	-	-	-	-	-	-	11771.1%
Cost of Revenues	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$1,148.9
Gross Income	$1,652.5	$0.0	$0.0	$0.0	$0.0	$0.0	$64.5	$6,510.3
Gross Margin	-	-	-	-	-	-	-	85.0%
R&D	$8,055.8	$1,288.6	$1,328.9	$1,452.2	$1,667.8	$5,737.5	$6,874.2	$8,212.9
% R&D	487.5%	-	-	-	-	-	10654.5%	107.2%
SG&A	$4,441.4	$976.2	$1,146.2	$1,201.7	$1,157.9	$4,482.0	$5,865.7	$6,648.5
% SG&A	268.8%	-	-	-	-	-	9091.4%	86.8%
Operating Income	($10,844.7)	($2,264.8)	($2,475.1)	($2,653.9)	($2,825.7)	($10,219.5)	($12,675.4)	($8,351.1)
Operating Margin	-656.3%	-	-	-	-	-	-19645.9%	-109.0%
Total, other income (exp)	$119.3	$39.6	$31.4	$25.5	$18.7	$115.2	$88.7	$110.8
Pre-Tax Income	($10,725.4)	($2,225.2)	($2,443.7)	($2,628.4)	($2,807.0)	($10,104.3)	($12,586.7)	($8,240.3)
Taxes	$86.0	$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	($10,811.4)	($2,225.2)	($2,443.7)	($2,628.4)	($2,807.0)	($10,104.3)	($12,586.7)	($8,240.3)
YOY Growth	-	-	-	-	-	-	-	-
Net Margin	-	-	-	-	-	-	-	-
EPS	($0.30)	($0.05)	($0.06)	($0.06)	($0.06)	($0.23)	($0.23)	($0.14)
YOY Growth	-	-	-	-	-	-	-	-
Diluted Shares O/S	35,484	43,702	43,800	43,912	44,021	43,859	55,000	60,000

Brian Marckx, CFA

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APPENDIX (for background only, may not be current)

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.[3] 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).

[3] 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.

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

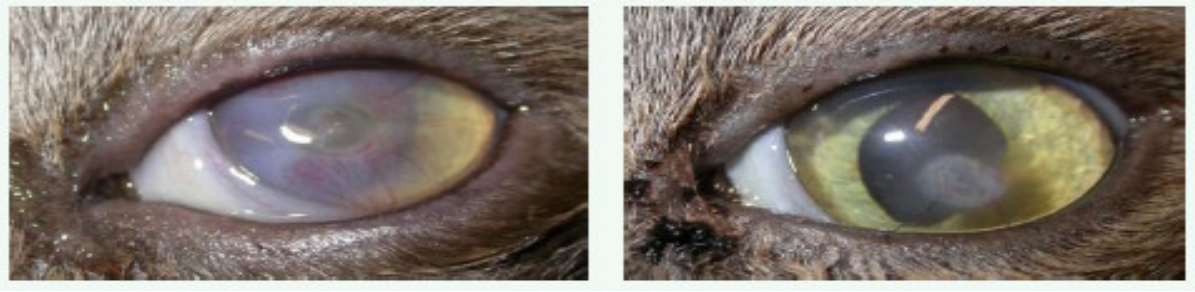
Initial Indication…

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

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

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

Non-healing corneal defect at 35 days (L) and healed (R) after 10 days of CMHA-S 0.75% treatment[4]



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



[4] Jade Therapeutics, Eyegate Pharmaceuticals

HISTORICAL STOCK PRICE



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