March 3, 2014

**OUTPERFORM**

Reason for report:

**INITIATION**

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# ELEVEN BIOTHERAPEUTICS, INC.

## Potential Blockbuster Dry Eye Drug Drives $24 PT; Initiate OP

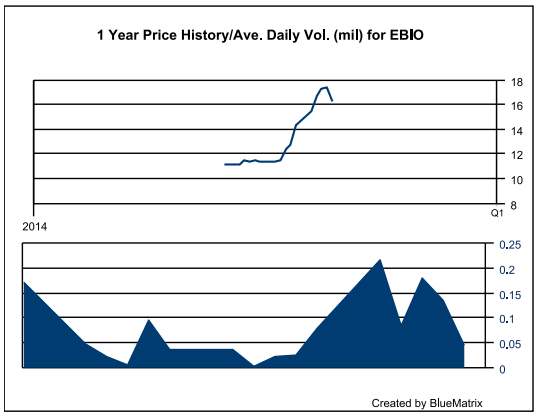
• **Bottom Line:** We are initiating coverage of EBIO with an Outperform rating – we expect that the shares will appreciate upon receipt of Ph. 3 top-line data for EBI-005 for treatment of dry eye disease (DED), most likely in early 2015. The market for dry eye disease therapy is large, and there remains a paucity of topical anti-inflammatory drugs that are both potent and tolerable. Based on improved understanding of the pathophysiology of dry eye, EBI-005 was developed to inhibit IL-1, which if left unchecked will promote expression of the other key inflammatory factors that exacerbate dry eye. Lastly, '005 has the potential to be a very long-tailed asset, with pending patents projected to expire in 2034, and '005 could enjoy additional exclusivity owing to the fact that it is a biologic. We forecast '005 sales of ~$550m by 2023, and our risk-adjusted DCF price target of $24/share assumes a 55-60% probability of success.

• **The market oppty for EBI-005 is substantial.** The market for dry eye is substantial, with at least 5m adults suffering from the condition and potentially as many as 9m pts. There are currently 1m pts on AGN's (MP) Restasis, but feedback from physician specialists indicates many pts have either discontinued Restasis due to tolerability issues or lack of efficacy. As such, we believe the commercial opportunity is substantial for a potent drug that targets the underlying systemic cause of the disease that is also tolerable for patients. Further, we view the recent Orange Book listing of Restasis patents as favorable for DED market pricing. With a couple of late-stage competitors in the pipeline, we forecast '005 to gain ~20% share if Ph. 3 is successful, which translates to $550m peak sales by 2023, & we believe the drug could continue to grow on price and category growth up through LOE in 2034.

• **Study design addresses several shortcomings with older drugs.** EBIO advanced '005 into pivotal trials on the basis of two studies, including a Ph. 1/2a safety trial. While the Ph. 1/2a was not powered to show efficacy vs. vehicle and only included ~20 patients per arm, the results did show numeric trends & informative post-hoc findings favoring '005. The first Ph. 3 study, OASIS-1, recently started and was designed keeping in mind some of the pitfalls of past development approaches, including the use of an environmental chamber, the use of broad, non-selective symptom based endpoints and restricting the use of rescue artificial tears in Ph. 3, which appears to have dampened the '005's efficacy signal in the earlier Ph. 1/2a safety trial.

• **Pivotal studies aren't without risk, but several encouraging factors suggest '005 should work on DED.** Bottom line - dry eye drugs have had a low success rate in pivotal trials and SHPG's (OP) lifitegrast is the latest example. Ophthalmology KOLs we spoke with were encouraged by the magnitude of effect size and the sizeable discrepancy in use of rescue tears in the control arm. In addition - the KOLs view '005 as having a solid mechanistic rational for treatment of DED and view selection of a narrower pain-based symptom endpoint as a good strategy for '005.

| **Key Stats:** | **(NASDAQ:EBIO)** |
|---|---|
| **S&P 600 Health Care Index:** | **1,293.35** |
| **Price:** | **$16.20** |
| Price Target: | $24.00 |
| Methodology: | DCF analysis |
| 52 Week High: | $19.33 |
| 52 Week Low: | $10.00 |
| Shares Outstanding (mil): | 15.4 |
| Market Capitalization (mil): | $249.5 |
| Book Value/Share: | $0.00 |
| Cash Per Share: | NA |
| Dividend (ann): | $0.00 |
| Dividend Yield: | 0.0% |




| Dec Yr | 1Q | 2Q | 3Q | 4Q | FY Rev | 1Q | 2Q | 3Q | 4Q | FY EPS | P/E |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **2013E** | 0.0A | 0.0A | 0.0A | 0.0 | 0.0 | ($0.08)A | ($0.09)A | ($0.09)A | ($0.08) | ($0.39) | NM |
| **2014E** | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | ($0.36) | ($0.48) | ($0.56) | ($0.56) | ($1.96) | NM |
| **2015E** | -- | -- | -- | -- | 0.0 | -- | -- | -- | -- | ($1.44) | NM |

*Source: Company Information and Leerink Partners LLC Research*

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ELEVEN BIOTHERAPEUTICS

# EBIO Initiation of Coverage Report

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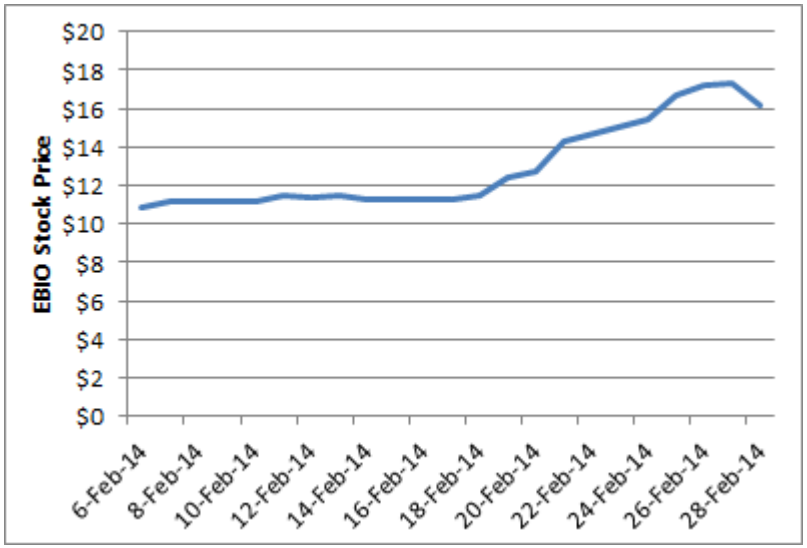
# Eleven Biotherapeutics (EBIO): Outperform

Rating: Outperform

Current Price: $16.20

Leerink PT: $24.00

Market Cap: $249M




*Source: Factset*

Leerink Estimates

| LP Estimates | EBIO Revenue | GAAP Diluted EPS |
|---|---|---|
| 2017E | 36 | ($2.89) |
| 2018E | 112 | $0.54 |
| 2019E | 180 | $3.19 |

Investment thesis: We are initiating coverage of EBIO with an Outperform rating – we expect that the shares will appreciate upon receipt of Ph. 3 top-line data for EBI-005 for treatment of dry eye disease, most likely in early 2015. The market for dry eye disease therapy is large and there remains a paucity of topical anti-inflammatory drugs that are both potent and tolerable. Based on improved understanding of the pathophysiology of dry eye, EBI-005 was developed to inhibit IL-1, which if left unchecked will promote expression of the other key inflammatory factors that exacerbate dry eye. Lastly, '005 has the potential to be a very long-tailed asset, with pending patents projected to expire in 2034 and '005 could enjoy additional exclusivity owing to the fact that it is a biologic. We forecast '005 sales of ~$550m by 2023 and our risk-adjusted DCF price target of $24/share assumes a 55-60% probability of success (POS).

Valuation: Our ~$24 price target on EBIO shares is based on our risk-adjusted DCF through 2034 discounted at 15% WACC. Using our sales forecasts and applying a 5x multiple to 2023 sales (year of peak market share) discounted back 9 periods at 15% WACC & 55% POS translates to $24. Our current valuation is solely predicated on EBI-005 for dry eye and we view label expansion to allergic conjunctivitis as upside.

Risks to Valuation: (1) EBI-005 drives our valuation and failure to demonstrate efficacy in Phase 3 trials would significantly reduce our valuation; (2) pipeline competitors develop more competitive product profiles, making it difficult for '005 to capture market share; and (3) generic threats to AGN's Restasis somehow materialize, making pricing/reimbursement for DED drugs more challenging.

# To Date, EBIO Has Outperformed the Market & Recent Biopharma IPO's

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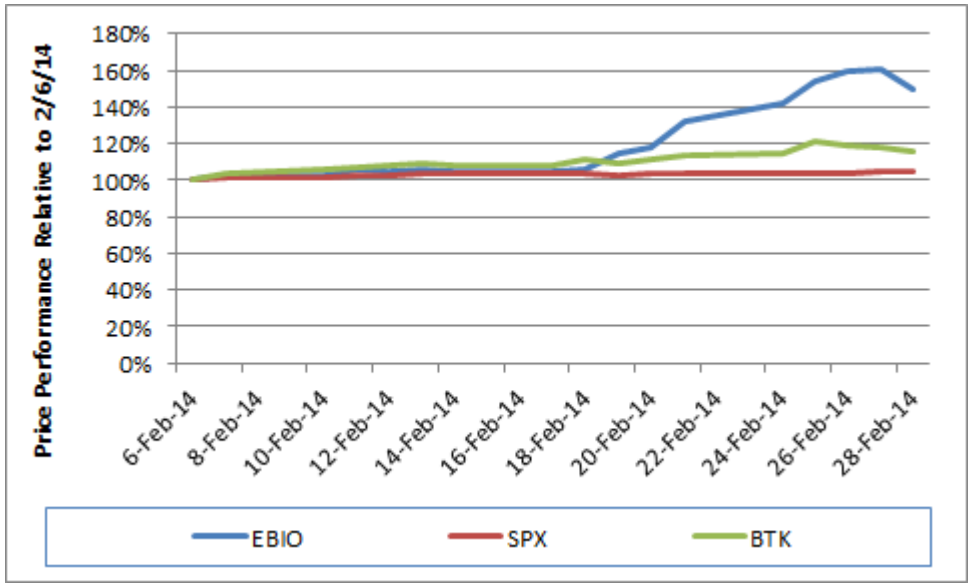
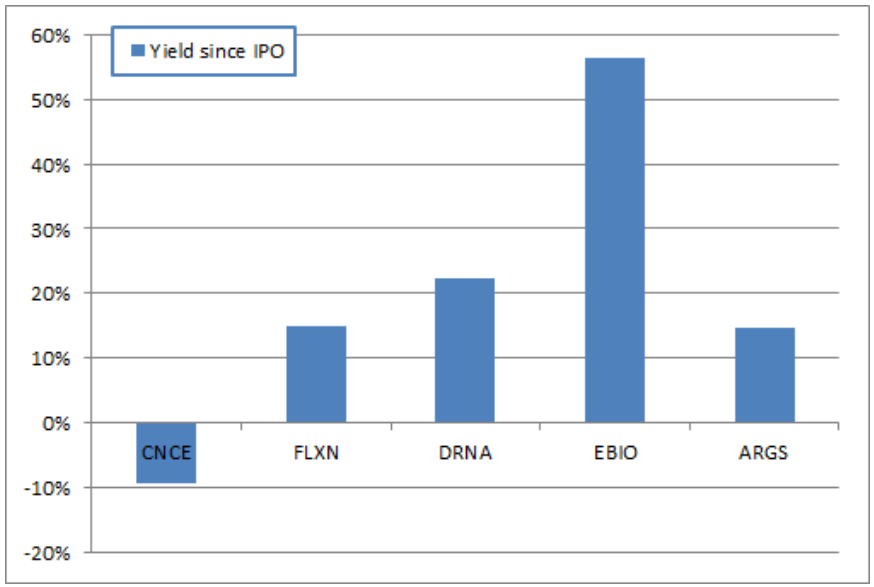
- On Feb. 6, shares of EBIO were listed on the NASDAQ Global Market . Pricing of 5m common shares IPO (initial public offering) was set at $10/share. Since the IPO, EBIO shares have outpaced the market by ~45% and the biotech index by ~35%. Relative to other biopharma IPO's in 2014, EBIO has generated a more favorable yield year-to-date.

## EBIO stock performance post IPO




*Source: FactSet*

## Performance Relative to Rest of 2014 IPO Class




*Source: FactSet*

# EBIO Description: Development Stage Company With Targeted Approach to Diseases of the Eye

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- **Company summary**: EBIO is a biopharmaceutical company with a proprietary protein engineering platform, called AMP-Rx, that is applied to discovery & development of protein therapeutics to treat diseases of the eye. The company's lead drug, EBI-005, was designed from the AMP-Rx platform and is being developed as a topical treatment for dry eye disease and allergic conjunctivitis. On 2/18, EBIO initiated a Phase 3 study of EBI-005 for treatment of moderate to severe DED, the OASIS study. The company plans to initiate its second Phase 3 study, but hasn't decided whether that study will initiate before or after the first pivotal study reads out. EBI-005 inhibits IL-1, an upstream mediator that blocks several important inflammatory factors believed to cause dry eye disease, which may be preferable to the mechanism of action of competitor drugs like Restasis. EBIO will also initiated a Phase 2 study looking at EBI-005 for treatment of severe allergic conjunctivitis starting sometime in 2014.

- **History of EBIO**: The company was founded in 2008 and the current CEO (Abbie Celniker) joined in Sept. 2011. The cornerstone of EBIO's biologic approach is based on the research of one of the company's scientific co-founders, Dr. Reza Dana. In 2013, the results of Dana's positive anti IL-1 for DED proof-of-concept study were published in a peer-reviewed journal – JAMA Ophthalmology. EBIO recently completed a Phase 1a/2b clinical trial using the commercial formulation of EBI-005 in patients with moderate to severe dry eye disease. Subsequently, EBIO decided to raise ~$60m through an initial public offering. The proceeds from the IPO will fund Ph. 3 development costs of EBI-005 in dry eye and Ph. 2 costs in allergic conjunctivitis



Source: Leerink .

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# Knowledgeable Management Team

- Abbie Celniker (CEO since 2011)
  - Previously CEO at Taligen Therapeutics, which was acquired by Alexion in 2011; prior to Taligen, Dr. Celniker was global head of biologics at Novartis, where she oversaw the biologics division and led internal discovery and development to build the pipeline
- Eric Furfine (CSO since 2011)
  - Previously Senior VP of Research & Preclinical Development at Adnexus, a Bristol-Myers Squibb R&D company; over 20-years of drug R&D experience
- Michael Goldstein (Head of Medical Research since 2010)
  - Drives EBIO's medical research and also serves as co-director of the Cornea, External Disease & Cataract Service group at Tufts University; Board certified ophthalmologist, has conducted clinical research throughout his career
- John McCabe (Head of Finance & Ops since 2012)
  - Previously VP of Finance at Clinical Data, Inc, which was acquired by FRX. Prior to Clinical Data, Mr. McCabe served several financial roles at Interleukin Genetics and Satcon. Mr. McCabe has 20 years of finance & accounting experience

# Key Investment Issues

- **We expect EBIO shares to outperform the market over the next 12-months due to:**
  - **Favorable risk/reward heading into readout of pivotal data**. Based on strong clinical activity in Phase 2, an optimized pivotal trial design, and a solid mechanistic rationale, we believe EBI-005 for dry eye is more likely to succeed in pivotal trials. As such, we forecast a 55-60% probability of clinical success.
  - **Blockbuster potential in market with unmet needs.** The market for dry eye is substantial with at least 5m pts seeking pharmacotherapy and 1m on the only approved topical anti-inflammatory drug. However, treatment rates are low due to suboptimal treatment options and we believe a successful drug could achieve blockbuster status given limited competitive environment.
  - **If approved, EBI-005 is biologic with potential to contribute well beyond targeted patent exclusivity period**. '005 has pending composition and formulation patents that expire in 2031 and 2034, respectively. In addition, '005 is a recombinant protein and barriers to generic entry for biologic therapy could remain high when the patents expire, meaning '005 could enjoy a longer exclusivity period.

- We forecast EBI-005 achieving peak market share by 2023, or ~$550m in US sales. We believe the drug can continue to grow beyond 2023 based on price and category growth and forecast the drug reaching ~$650m by 2030. Currently, there is no sell-side consensus for EBIO sales,

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# DCF Analysis Suggests a $24/share Valuation for EBIO

| | |
|---|---|
| Shares Outstanding | 15.8 |
| Net cash, EOY '14 | 23 |
| Discount Rate | 15% |

| EBIO | POS | NPV | Risk adj | Per shr |
|---|---|---|---|---|
| EBI-005 | 57.5% | 606 | $348 | $22 |
| Cash, EOY '14 | 100% | 23 | $23 | $1 |
| **Total** | | | | **$24** |

| EBI-005 | 2014E | 2015E | 2016E | 2017E | 2018E | 2019E | 2020E | 2021E | 2022E | 2023E | 2024E | 2025E | 2026E | 2027E | 2028E | 2029E | 2030E | 2031E | 2032E | 2033E | 2034E |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sales | - | - | - | 36 | 112 | 180 | 265 | 367 | 465 | 562 | 583 | 605 | 628 | 634 | 639 | 644 | 649 | 654 | 659 | 665 | 670 |
| Gross profit | - | - | - | 31 | 98 | 162 | 238 | 331 | 419 | 505 | 525 | 545 | 566 | 570 | 575 | 579 | 584 | 589 | 593 | 598 | 603 |
| G&A | 4 | 4 | 4 | 18 | 20 | 21 | 23 | 25 | 26 | 28 | 30 | 32 | 34 | 37 | 39 | 42 | 45 | 48 | 52 | 55 | 59 |
| R&D | 27 | 22 | 22 | 18 | 14 | 15 | 15 | 16 | 16 | 17 | 17 | 18 | 18 | 19 | 14 | 15 | 16 | 16 | 17 | 18 | 18 |
| S&M | - | - | - | 55 | 54 | 57 | 60 | 63 | 66 | 69 | 73 | 76 | 80 | 84 | 88 | 93 | 97 | 102 | 107 | 113 | 118 |
| **Operating income** | **(30)** | **(26)** | **(26)** | **(60)** | **11** | **69** | **140** | **228** | **310** | **392** | **405** | **419** | **433** | **431** | **433** | **430** | **426** | **422** | **417** | **412** | **407** |
| **% Op margin** | nm | nm | nm | -164% | 10% | 38% | 53% | 62% | 67% | 70% | 69% | 69% | 69% | 68% | 68% | 67% | 66% | 65% | 63% | 62% | 61% |
| Non-operating expense | (1) | (1) | (1) | (1) | 1 | 1 | 2 | 3 | 4 | 5 | 10 | 11 | 12 | 13 | 14 | 15 | 15 | 15 | 15 | 15 | 15 |
| Tax expense | - | - | - | - | - | - | - | 81 | 110 | 139 | 145 | 150 | 156 | 155 | 156 | 156 | 154 | 153 | 151 | 150 | 148 |
| **Free Cash Flows** | **(31)** | **(26)** | **(27)** | **(60)** | **12** | **70** | **142** | **150** | **204** | **258** | **270** | **279** | **289** | **288** | **290** | **289** | **287** | **284** | **281** | **278** | **274** |
| Discount periods | - | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
| **PV FCF** | **(31)** | **(23)** | **(20)** | **(40)** | **7** | **35** | **61** | **56** | **67** | **73** | **67** | **60** | **54** | **47** | **41** | **36** | **31** | **26** | **23** | **20** | **17** |

*Source: Leerink Research ests*

| Scenario Analysis | base | bull | bear |
|---|---|---|---|
| % Peak EBI-005 | 20% | 25% | 15% |
| DCF | $24 | $33 | $14 |
| EBI-005, 2023 sales | 562 | 702 | 421 |

*Note: Lone variable changed was EBI-005 share*

Scenario Analysis illustrates sensitivity of DCF calculation to EBI-005 market share assumptions

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# EBIO Pipeline & Upcoming Events

| Program | Target | Platform | Partner | Indication | Current status | Next milestone | Timing |
|---|---|---|---|---|---|---|---|
| EBI-005 | IL-1 | AMP-Rx | none | Dry eye disease | Ph. 3 ready | Ph. 3 data (OASIS-1) | Early '15 |
| | | | | | | Inititiate Second Ph. 3 | 2H'14 or 1Q'15 |
| | | | | | | Ph. 3 data (OASIS-2) | Late '15 or 1Q16 |
| | | | | | | BLA submission | End of '16 |
| | | | | | | Est. US launch | 2017 |
| | | | none | Allergic conjunctivitis | Phase 2 | Initiate Ph. 2 | 2014 |
| | | | | | | Ph. 2 data | Early '15 |
| EBI-029 | IL-6 | AMP-Rx | none | Diabetic macular edema | Preclinical | Initiate Ph. 1 | TBD |
| EBI-028 | IL-17 | AMP-Rx | none | Uveitis | Preclinical | Initiate Ph. 1 | TBD |

*Source: EBIO S-1 statement*

EBIO's key catalysts will be top-line Phase 3 data for lead drug EBI-005

# EBI-005 for Dry Eye Disease

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# EBIO-005 (dry eye) Opportunity: Cheat Sheet

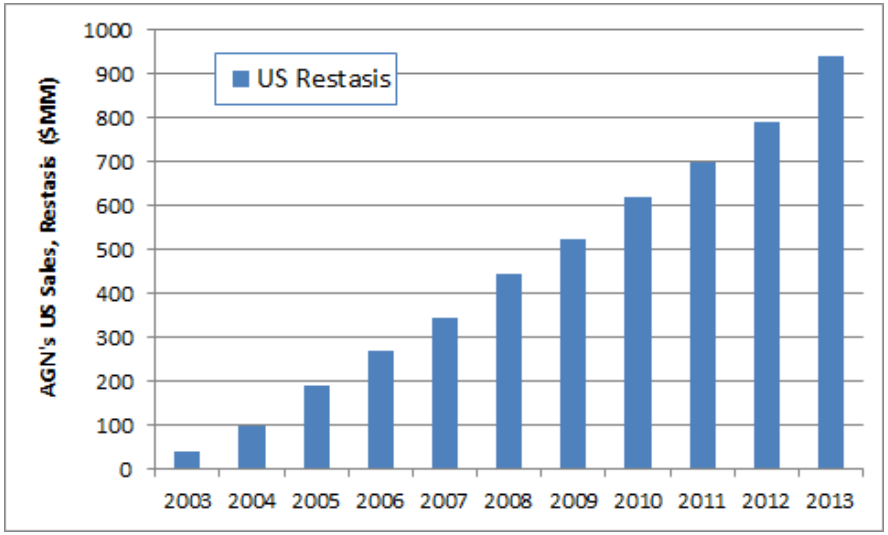
## Background

- **Product description**: EBI-005 is a recombinant protein that binds to IL-1 (interleukin-1) receptor and blocks IL-1 signaling to many cell types in the eye. '005 is a topical eye drop treatment that is administered three-times daily and is room temperature stable. According to EBIO, '005 was developed using a "comfortable vehicle" to enhance tolerability of the drug (vehicle undisclosed).
- **Product history**: In 2012, EBIO began conducting clinical trials of '005 using the commercial formulation. In Sept. 2013, EBIO reported positive top-line results from a Phase 1/2a study, which along with a randomized study (Reza study) looking at a compounded version of IL-1 blockade for DED served as the basis for advancing the program into Phase 3, which started in Feb. 2014. EBIO holds exclusive, worldwide commercialization rights on '005.
- **Dry eye markets**: The primary market for branded DED therapy is in the US, although there is an opportunity for geographical expansion. US prevalence ests are highly variable and range from 5m to 25m pts suffering from DED and epidemiologists expect the disease to increase with age. Currently, ~1m pts (~$910m in '13 sales) receive the only branded Rx therapy, AGN's Restasis. We view the 1m figure as a firm anchor for market sizing purposes, but, as we highlight in this report, physician specialist feedback suggests the market could expand if more/better treatment options became available. Treatment options for DED include: (1) artificial tears, which are sold over-the-counter; (2) topical steroids – which have toxicities limiting usage; & (3) branded anti-inflammatory, which include AGN's Restasis and several Ph. 3 drugs, including SHPG's lifitegrast and EBIO's '005.
- **Intellectual property**: '005 patents include: (1) filed composition of matter patents, which if granted would provide protection until 2031; (2) a provisional formulation patent, which if granted would expire in 2034; (3) patent cooperation treaty application expected to expire in 2033. EBIO also has method of use patents filed with similar expiries.
- **Development stage label expansion opportunities**: EBIO is exploring additional indications for '005, including allergic conjunctivitis, which will move into Ph. 2 later this year.

## How '005 works

- **Description of mechanism**: (1) Desiccating stress induces secretion of inflammatory cytokines including IL-1, facilitating migration of antigen presenting cells (APCs) towards draining lymph node, (2) APCs stimulate naïve T cells leading to Th17 cells, which secrete IL-17, (3) effectors migrate to ocular surface and secrete effector cytokines; interaction of IL-17 with receptors leads to epithelial damage. IL-1 blockade upregulates key inflammatory mediators of DED like IL-6 and LFA-1 and may control lymphangiogenesis – which would check the bulk of inflammatory mediators similar to steroids without the dose limiting toxicity.

## Restasis US annual revenue history




*Source: AGN reported sales*

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# Background on Dry Eye Disease

- **Cause:** Dry eye disease (DED) is classified as a condition of tear insufficiency secondary to decreased tear production, increased tear evaporation or a combination of both. DED is caused by a disturbance of the lacrimal function unit (LFU), an integrated system comprising the lacrimal glands, ocular surface and lids, and the sensory and motor nerves that connect them. The LFU controls the major components of tear film in a regulated fashion and responds to various environmental, endocrinological and cortical influences. The overall function of the LFU is to preserve the integrity of tear film, the transparency of the cornea and the quality of the image projected onto the retina. Disease or damage to any component of the LFU can result in DED, but the core mechanism of DED is driven by tear hyperosmolarity and tears film instability.

- **Most common disease indicators:** There are several tests and procedures used to determine if a patient has DED, including: (1) a comprehensive eye exam; (2) measuring volume of the pts tears – using a Schirmer test; & (3) assessment of quality of pts tears – use of special dyes in eyedrops to determine surface condition of pts eyes, which can include staining patterns on the cornea and measurement of time for tears to evaporate

- **Symptoms:** The most common symptoms are burning, itching, scratching, foreign body sensation, photophobia and red eye.

- **Goals of pharmacotherapy:** General goal is to treat the underlying systemic disease, if any, and eliminate causative factors that may contribute to DED. An important causative factor is inflammation, which an International Task Force of panelists agreed either triggers or sustains most cases of DED, even in cases where inflammation is not apparent. As such, topical anti-inflammatory therapies (corticosteroids & topical cyclosporine) are recommended beginning where patients have moderate-to-severe symptoms. Short courses (2-4 weeks) of topical corticosteroids are used to provide symptomatic improvement, but long-term use is limited by steroid-related side effect concerns. In clinical practice, topical cyclosporine is viewed as a better long-term therapy given that it is not associated with either significant systemic SE's or the common steroid-related SE's.

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# Comparison of Therapeutic Approaches

## Current & Development-Stage Treatment Options

| Drug Class | Treatments | Appropriate to treat | Pros | Cons |
|---|---|---|---|---|
| Artificial tears | Numerous varieties, including sustained moisture – methylcellulose, lubricant, preservative free unit doses | Mild DED | Cheap, safe/tolerable, provides short term symptom relief | Modest efficacy, doesn't target underlying systemic disease |
| Topical steroids | Dexamethasone, soft steroids (Lotemax or Alrex) or hard steroids like Alcon's Durezol | Moderate to severe DED | Highly efficacious | Tox limits duration of use, need to wean pts off therapy |
| Topical antibiotic | Tobramycin, doxycycline, azithromycin, & tetracycline | Co-morbid infection | Alternative for DED pts susceptible to infection | Doesn't benefit DED symptoms |
| Topical cyclosporine | Restasis | Moderate to severe DED | Safe for long-term use & proven efficacy | Tolerability -- ocular burning and non-response in some pts |
| IL-1 blockage | EBI-005 | Moderate to severe DED | Favorable tolerability, room temp stability, fast onset | Yet to show stat sig efficacy |
| LFA-1 antagonist | Lifitegrast | Moderate to severe DED | Fast onset, first drug to show benefit on DED symptoms | Missed co-primary endpt in each of two pivotal Phase 3 studies |

*Source: Product Package inserts*

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# Several Development Stage Products for DED

**Review of DED Late Stage Pipeline (doesn't include steroids)**

| Drug (Company) | Drug Class | Stage of Development | Target Profile | Comments |
|---|---|---|---|---|
| Lifitegrast (SHPG) | LFA-1 antagonist | Phase 3 | BID, topical | Based on regulatory specialist feedback, we believe SHPG will need to conduct another Ph. 3 study to confirm a benefit on DED signs |
| EBI-005 (EBIO) | IL-1 blockade | Phase 3 | 3x-day, topical | |
| Rebamipide (Acucela/Otsuka) | Stimulates prostaglandin generation | Phase 3 | 4x-day dosing, topical | Approved for sale in Japan; several Ph. 3's completed in in 2006-08 timeframe, another Ph. 3 completed in June 2013 |
| MIM-D3 (Mimetogen/VRX) | TrkA agonist | Phase 3 | BID, topical | B&L acquired an option on the Ph. 3 ready drug in July 2013 after Mimetogen reported Phase 2 data. In the Ph. 2, the pre-specified primary endpts were not met, but the drug showed activity in post-hoc analysis. Primary completion for data collection June 2014 |
| CF101 (OphthaliX) | A3 adenosine receptor agonist | Phase 3 | Oral | On Dec. 30, 2013, OphthaliX announced CF101 missed its primary endpt on corneal staining and missed its secondary endpts |
| R9348 (Rigel) | Jak/Syk inhibitor | Phase 2 | BID, topical | CFS staining endpt in study that will complete in July 2014 |
| AGN-195263 (Allergan) | Undisclosed | Phase 2 | BID, topical | Appears to target meibum gland, which produces the oily layer of tear film |

*Source: Product Package inserts*
*Notes: BID = twice daily dosing*

# SHPG's Lifitegrast Is the Primary Pipeline Threat, But Regulatory Pathway for the Drug Is Unclear

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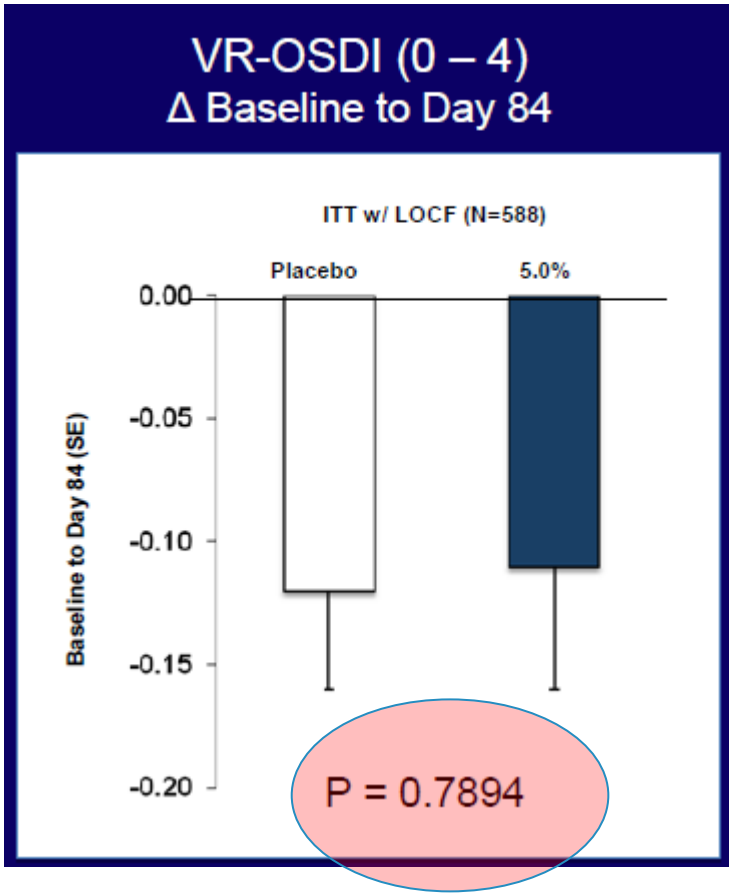
## First pivotal study (OPUS-1) missed symptom co-primary endpoint




Source: Sheppard et al. (OPUS-1 presentation)

## Second pivotal study (OPUS-2) missed sign Co-primary endpoint

**From Dec. 5, 2013, press release:** Lifitegrast did not meet the pre-specified co-primary endpoint for the sign of **inferior corneal staining score** (change from baseline to Week 12) using fluorescein staining compared with placebo (p value=0.6186)

Source: Shire press release, 12/5/2013

# US Dry Eye Market Is an Attractive Commercial Oppty

- **Disease prevalence ranges from 5-25m US patients suffering from dry eye disease. The prevalence is expected to increase as the population ages.**

- **But only 1m patients receive branded prescription therapy**, due to (1) a paucity of approved treatment alternatives; and (2) weak efficacy and poor tolerability of the lone approved treatment, AGN's Restasis
  - Restasis ocular burning occurred in 17% of study subjects, but physician specialist report a much higher rate (20-40%) in practice

- **Treatment rates likely to expand, based on**
  - **Feedback from physician specialists** who believe the market for branded prescription therapy could be significantly larger if an efficacious and more tolerable treatment alternative were available
  - **More players in the market should improve awareness and provide a wider range of alternatives**

- **Pricing is relatively attractive – the current "net price" per Restasis prescription is $300, or $10/day.** With AGN recently getting newly listed Orange Book patents that expire in 2024, we expect pricing & reimbursement in the dry eye market to remain healthy for the foreseeable future

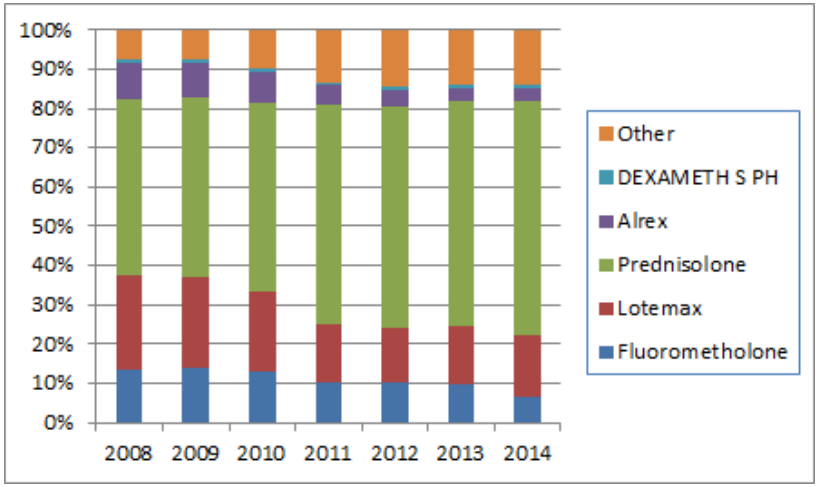
- **Label expansion into severe allergic conjunctivitis represents an upside opportunity** for investors. The disease is currently managed by anti-histamines & mast cell stabilizers, while treatment options for more severe/refractory pts is limited

# DED Prescription Data Partially Validates High Prevalence Estimates

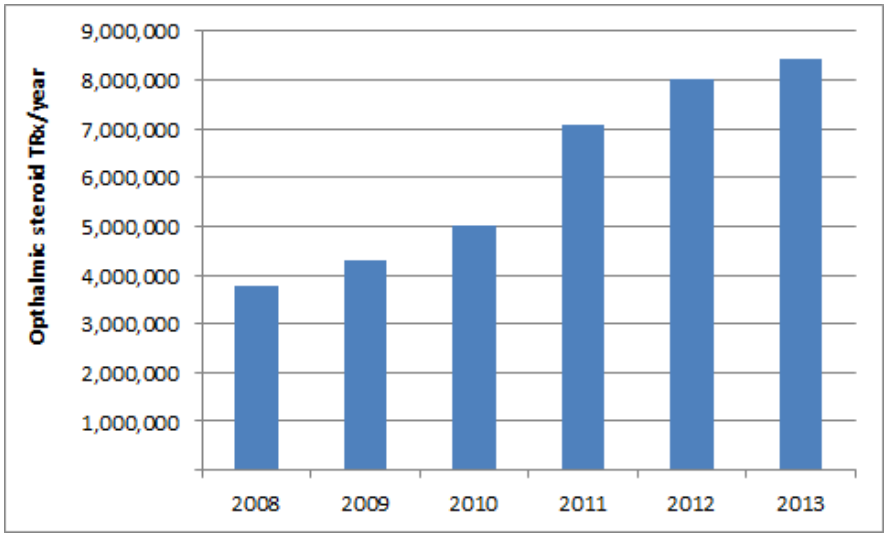
## Background

- **US Market Size**: We focus on three data points: (1) US prevalence ests ranging from 5-25m; (2) AGN's Restasis - ~$910m in '13 sales from ~3m prescriptions; & (3) brand volumes from topical ophthalmic steroids and Restasis. We summarize the available IMS prescription data for DED products on this slide.
- **Ophthalmic steroid market provides a decent proxy for market volume**, but the issue is that prednisolone is a multi-use steroid that dominates by volume share and gets used frequently outside of DED. On the bottom right, we est ~6m prescriptions are written for commonly used topical ophthalmic steroids (excluding prednisolone) and anti-inflammatory Restasis. However – not all the topical steroid scripts are written for DED, so take the data with a grain of salt.

## Market Share of Opth Steroid Brands

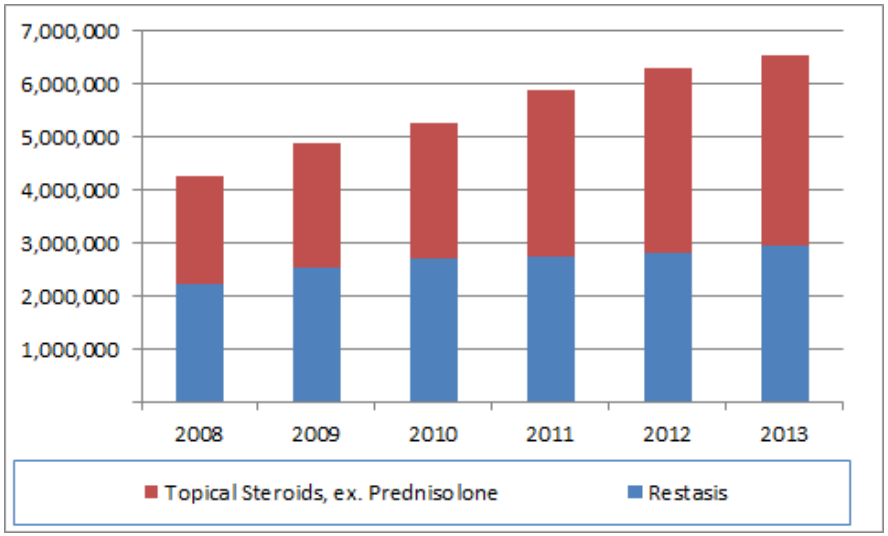



## US Ophthalmic Steroid – Annual TRx




*Source: IMS (USC code 61411 & Alrex)*

## US Scripts for steroids + Restasis




*Source: IMS*

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# EBI-005 for Treatment of DED

- **EBI-005 is a recombinant protein that binds with the IL-1 receptor and blocks IL-1 signaling on many cell types in the eye**. Sobi's Kineret (anakinra) is a marketed, subcutaneous version of anti IL-1 for treatment of rheumatoid arthritis.

- Based on reported data, EBI-005 may offer the following benefits to dry eye patients:
  - Clinically meaningful magnitude of benefit
  - Benefit on both signs and symptoms
  - Rapid onset of effect – benefit seen between week 2-6
  - Reduced artificial tear use in clinical trials

- **Summary of reported clinical data:** EBIO did not power its Phase 1b/2a trial to measure efficacy with statistical significance, and the differences from baseline that were observed in the EBI-005 treatment groups were not statistically significant when compared to differences from baseline in patients who received vehicle control. However, the company did see encouraging signs of drug activity including:

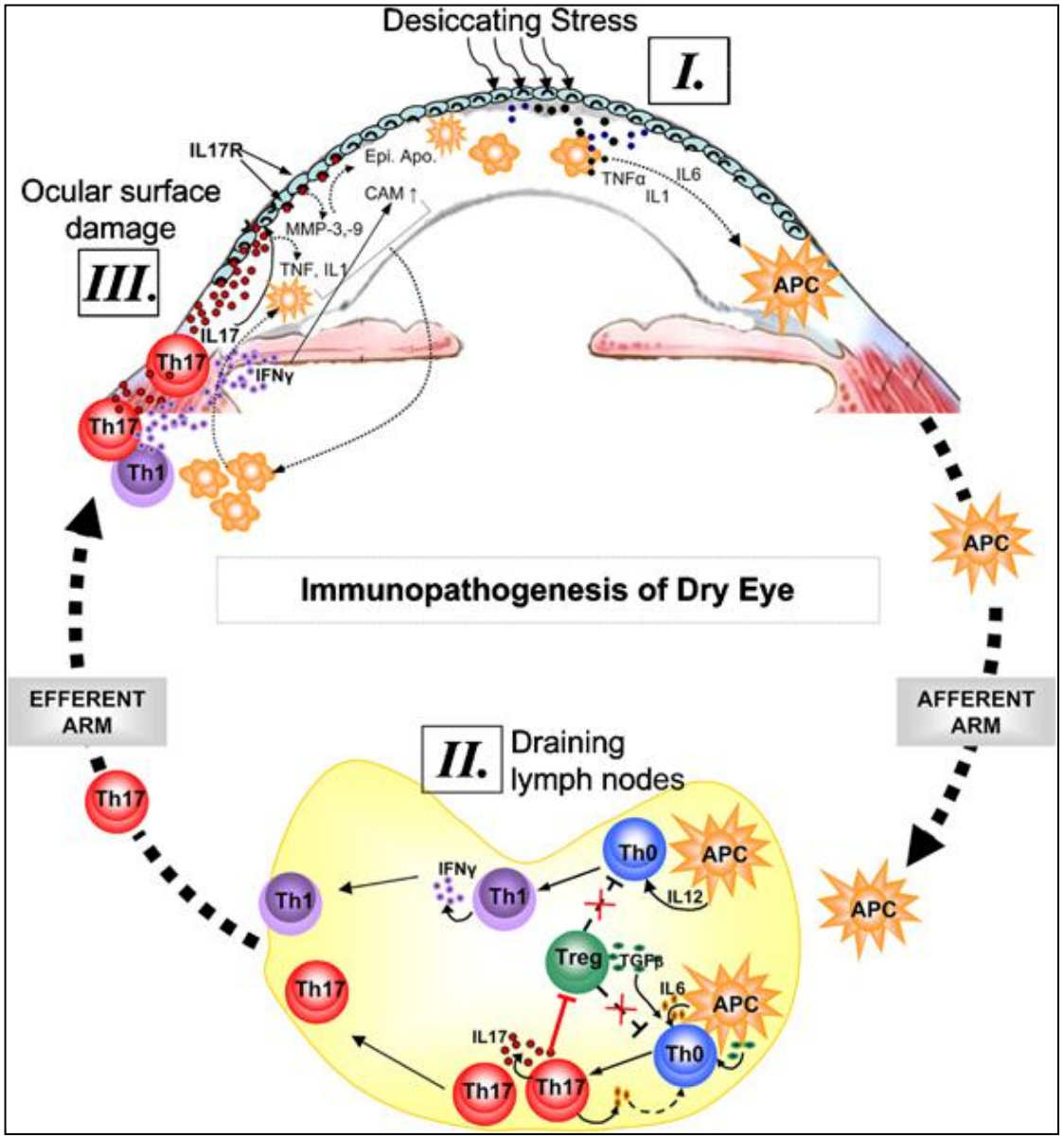
  - **Signs of disease (corneal staining score)** in a small 75 patient study looking at safety/tolerability, EBIO's founders observed 20-45% improvements relative to baseline using the topical formulation of Anakinra. In another study (Ph. 1b/2a), EBI-005 showed a 33% improvement from baseline on disease signs ($p<0.001$)

  - **Symptoms of disease –** in Ph. 1a/2b, EBI-005 showed a 36% improvement from baseline ($p<0.001$) while in the Reza study week 12 symptom reduction (vs. placebo) ranged from 30-35%

  - **Onset of action may be an advantage –** symptom reduction was seen in Reza study as early as week 2 and reached statistical significance compared to vehicle by week 6

  - **Low use of rescue tears –** in the Ph. 1a/2b study, the median number of rescue tears (measured in vials) was 10.5 for the vehicle group versus 1 for the EBI-005 group

# IL-1 Blockade – A Logical Target for Dry Eye Disease




Source: S K Chauhan and R Dana, Mucosal Immunology (2009)

- **Dry eye disease is classified as a condition of tear insufficiency secondary to decreased tear production, increased tear evaporation or a combination of both.** Factors that adversely affect tear film stability and osmolarity can induce ocular surface damage and initiate an inflammatory cascade that generates innate and adaptive immune responses
- **Pathway**: (1) Desiccating stress induces secretion of inflammatory cytokines including IL-1, facilitating migration of antigen presenting cells (APCs) towards draining lymph node, (2) APCs stimulate naïve T cells leading to Th17 cells, which secrete IL-17, (3) effectors migrate to ocular surface and secrete effector cytokines; interaction of IL-17 with receptors leads to epithelial damage
- IL-1 promotes expression of other inflammatory factors including LFA-1 and IL-6

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# EBI-005 Clinical Trial Summary Suggests a Highly Active Drug

| Ph. 2 comparison | EBI-005 Ph. 1a/2b | Anakinra study (Reza) |
|---|---|---|
| # of subjects | 74 randomized participants (EBI-005 5mg/mL, n=22, EBI-005 20mg/mL, n=22, placebo, n=30) | 75 randomized participants receiving 2.5% (n=30), 5% (n=15), or vehicle (1% carboxymethylcellulose) (n=30) |
| Key inclusion criteria | Minimum OSDI score of 23 and CFS score of 6 | 18+ with corneal or conjunctival epithelial staining (score ≥ 1) on the OGS; diagnosis of meibomian gland dysfunction |
| Treatment duration | 42 days (6 weeks), 3x daily | 84 days (12 weeks), 3x daily |
| Primary endpoint | (1) CFS, (2) OSDI | (1) CFS, (2) CFS clearance, (3) OSDI |
| Primary result | (1) CFS: 33% improvement vs. baseline, p<0.001, (2) OSDI [symptoms] 36% improvement vs. baseline, p<0.001 | (1) 2.5% Anakinra: a 46% reduction in mean CFS score (P = .12 vs. vehicle and P <.001 vs. baseline); 5%: a 17% reduction (P = .88 vs. vehicle and P = .33 compared vs. baseline); vehicle: a 19% reduction (2) 2.5%: complete bilateral CFS clearance in 8 of 28 patients (29% ), vehicle: 2of 29 patients (7%) (3) 2.5% Anakinra: a 30% reduction in OSDI, 5%: a 35% reduction; vehicle: a 5% reduction |
| Most frequent AE's | Of the 8 ocular AE's: 2 were in the vehicle treated eyes, 4 were in the 5 mg/mL treated eyes and 2 were in the 20 mg/mL treated eyes | No serious ocular or systemic adverse events attributable to treatment. 8 study drop outs (6 placebo pts vs. 2 drug pts). Discomfort related to drop instillation more common in pbo than drug arm. |

Source: Amparo et al., JAMA Ophthalmology (2013)

# OASIS Study Design Informed by Key Findings in Earlier Trials

| Study | OASIS | Rationale |
|---|---|---|
| **Trial Design** | 12-week, randomized, double masked, vehicle controlled, moderate to severe DED patients, 3x-day dosing, natural environment study | 12-week studies are customary in DED; the Ph. 1/2a trial was only 6-weeks, but EBIO believes Reza study validates activity of drug through 12-weeks. EBIO conducted its Ph. 1/2a in a natural environment rather than controlled adverse environment (chamber) which historically has been used in trials of product candidates for DED. EBIO is operating on the hypothesis that the controlled environment introduces differences in the presentation and manifestation of DED and in pts perception of their disease and EBIO ultimately believes this deviates from real world experience in which pts/physicians judge the benefit of the drug. |
| **Number of subjects** | 650 patients evenly randomized to EBI-005 5mg/mL (n=325) versus vehicle control (n=325). Study will occur at 40 treatment centers | Standard for DED pivotal studies |
| **Key inclusion criteria** | (1) OSDI score at screening >23 and <75, but pt must be <50 at randomization<br>(2) CFS score 6-15 at screening | EBIO will enroll moderate to severe pts. Based on retrospective analysis of Ph. 1/2a data, EBIO believes pts with OSDI >50 produce more variable and will therefore will exclude those pts at randomization of OASIS trial |
| **Key exclusion criteria** | Use of rescue artificial tears will be prohibited | In Ph. 1/2a, EBIO measured use of tears in a pre-specified exploratory endpt and found use of tears was meaningfully higher in the vehicle group, which the company believes may have impacted the efficacy data |
| **Primary endpt** | (1) corneal fluorescein staining score<br>(2) improvement in pain and discomfort (OSDI score) | In Ph. 1/2a, EBIO observed a trend of greater improvement of scores on the OSDI question of painful or sore eyes from baseline at week 6 |
| **Secondary endpt** | Total OSDI (chg from baseline to 12-week) | |

Source: Clinicaltrials.gov, EBIO S-1 statement

# Retrospective Analysis: Symptomatic Benefit Most Profound on OSDI-Pain

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As noted on the previous slide, EBIO saw a profound benefit on OSDI, which informed its primary endpt selection for the Phase 3 OASIS trial. In general, KOL specialists view broader OSDI questionnaires as more difficult to demonstrate efficacy given that pts generally don't report feeling the broad spectrum of symptoms listed. EBIO is operating under the assumption that IL-1 exerts an analgesic effect on the eye which is why OSDI-pain is best endpt for the drug

| | Painful or sore eyes question | | | |
|---|---|---|---|---|
| | Combined EBI-005 treatment groups | | Vehicle control group | |
| | EE population (n = 41) | EE50 population (n = 20) | EE population (n = 26) | EE50 population (n = 15) |
| Mean Score on OSDI Question at Baseline | 1.8 Points | 1.4 Points | 1.7 Points | 1.3 Points |
| Mean Change in Score on OSDI Question from Baseline to Week Six | 0.9 Points | 0.9 Points | 0.5 Points | 0.4 Points |
| Percentage Change in Score on OSDI Question from Baseline to Week Six | 46% | 61% | 27% | 31% |

Source: EBIO S-1 statement

# Efficacy Signal in Ph. 1/2a May Have Been Dampened by Lack of Restriction on Rescue Tears

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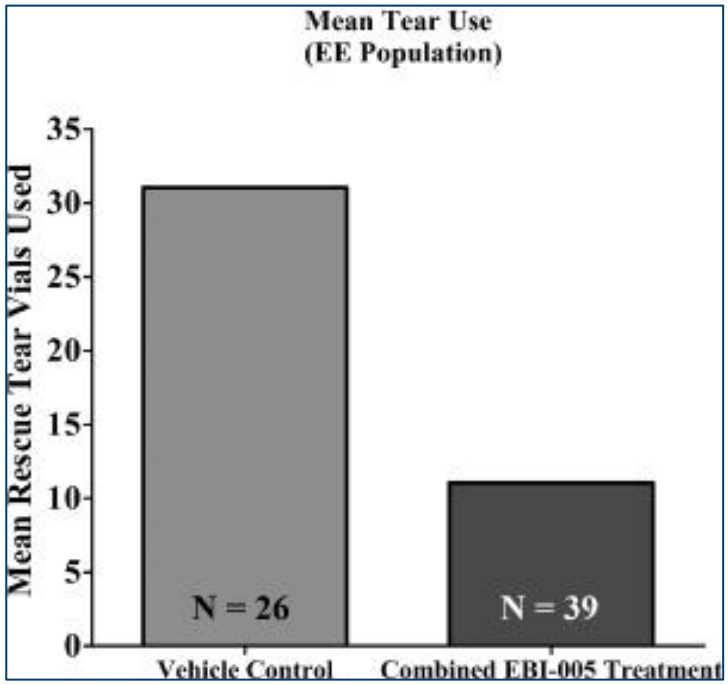
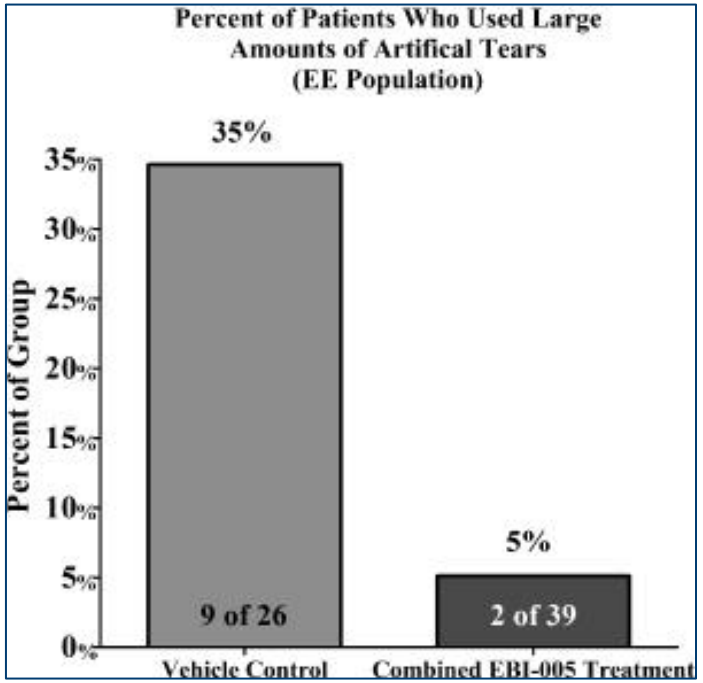
In a pre-specified exploratory analysis, mean artificial tear use was greater in the vehicle group (p=0.005) in efficacy evaluable population




Source: EBIO S-1 statement

# EBI-005 Looks Reasonably Well Tolerated & Has the Potential to Show Lower AE Rates in Pivotal Trials

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| Ocular Adverse Event Data | Vehicle (n=30) | EBI-005, 5mg/mL (N=22) | EBI-005, 20mg/mL (N=22) | EBI-005, 5+20 mg/mL (N=44) |
|---|---|---|---|---|
| Number of patients with one or more ocular adverse events | 0 (0%) | 1 (5%) | 2 (9%) | 3 (7%) |
| **Eye disorders** | | | | |
| Eye irritation | 0 (0%) | 0 (0%) | 1 (5%) | 1 (2%) |
| Eye pain | 0 (0%) | 1 (5%) | 1 (5%) | 2 (5%) |
| Foreign body sensation in eyes | 0 (0%) | 1 (5%) | 0 (0%) | 1 (2%) |
| Increased tearing | 0 (0%) | 1 (5%) | 0 (0%) | 1 (2%) |
| Ocular redness | 0 (0%) | 1 (5%) | 0 (0%) | 1 (2%) |

Source: EBIO S-1 statement

**AGN's Restasis showed a 17% rate of ocular burning in clinical trials**

**SHPG's lifitegrast also showed a very low rate of ocular AE's including burning in the 1-5% range in its Phase 2 trials**

# Intellectual Property

- **EBIO holds an exclusive worldwide license** to patent applications protecting anti-IL-1, including EBI-005, pursuant to a license agreement with Schepens Eye Research Institute. In connection with the license agreement, EBIO will pay Schepens an upfront licensing fee and are obligated to pay future milestone payments with respect to EBI-005 as well as a tiered royalty ranging from low-single-digit to mid-single-digit percentages of net sales

- According to the S-1, **EBI-005's pending patent applications** are composition of matter, method of use and formulation patents and the company has indicated the patents could extend to 2031-34

- **EBI-005 is a biologic** that is manufactured using recombinant processes, meaning it will be more challenging for generic drug companies to establish bioequivalence to EBI-005

- **Risk from compounded alternatives is low, in our view**: Anakinra (Sobi's brand Kineret), an IL-1 inhibitor that is approved for marketing in the United States and other countries for treatment of rheumatoid arthritis and is formulated for subcutaneous administration. Anakinra can be re-formulated, or compounded, for topical ophthalmic application.

# AGN's Restasis Market Looks Like It Will Remain a Branded Product Category for Foreseeable Future

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| Patent Number | Expiry | Type of Patent |
|---|---|---|
| 8,629,111 | Aug. 27, 2024 | A topical ophthalmic emulsion for treating an eye of a human comprising cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight |
| 8,633,162 | Aug. 27, 2024 | A method of treating dry eye disease, the method comprising topically administering to the eye of a human in need thereof an emulsion at a frequency of twice a day, wherein the emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; and wherein the topical ophthalmic emulsion is effective in treating dry eye disease |
| 8,642,556 | Aug. 27, 2024 | A first topical ophthalmic emulsion for treating an eye of a human, wherein the first topical ophthalmic emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; and wherein the first topical ophthalmic emulsion is therapeutically effective in treating dry eye disease; and<br>wherein the first topical ophthalmic emulsion provides overall efficacy substantially equal to a second topical ophthalmic emulsion comprising cyclosporin A in an amount of about 0.1% by weight and castor oil in an amount of about 1.25% by weight |
| 8,648,048 | Aug. 27, 2024 | method of increasing tear production in the eye of a human, the method comprising topically administering to the eye of the human in need thereof an emulsion at a frequency of twice a day, wherein the emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; and wherein the topical ophthalmic emulsion is effective in increasing tear production |

On Jan. 22, it was announced that ACT is developing a generic version of Restasis. Feedback from a MEDACorp patent specialist indicated generics won't be able to avoid infringing the '111 patent while still falling within the parameters of the FDA bioequivalence guidance for Restasis, which calls for generic formulation to be qualitatively and quantitatively the same as the brand

Source: Orange Book, google patents

# MEDACorp Physician Specialists' Comments on EBI-005

- **Target product profile:** (1) efficacy – KOLs view '005 as a drug with likely strong activity based on reported clinical data and physicians would like to see a 30% spread versus vehicle in pivotal study; (2) tolerability – reported ocular AE rates in low single digits is encouraging and '005 looks to have a good tolerability profile, but post-market experience with the drug could influence physician opinion; physicians we spoke with noted that clinical adverse event data for Restasis reportedly under calls the frequency of events in real world practice

- **Unmet need in DED market:** Physicians specialists believe current treatment options are lacking – noting the only approved topical anti-inflammatory drug, AGN's Restasis, (1) has real world ocular burning in 20-40% of their patients; and (2) response rates are suboptimal with many patients not responding to Restasis

- **Thoughts on EBI-005 clinical data:** (1) data were encouraging for a small study; (2) if 30% benefit is reproducible, that's better than any drug KOLs have seen; (3) quality of study perceived to be "pretty good" and lack of rescue tears were viewed to support hypothesis that '005 has favorable impact on pain; (4) tolerability data perceived as an improvement relative to Restasis. Ultimately – KOLs view '005's benefit on pain as unclear, noting the pathophysiology is uncertain but specialists suspect nerve endings are exposed during inflammation so any drug that reduces inflammation should theoretically reduce pain

- **Likelihood of demonstrating efficacy in pivotal trials:** Given low success rates of drugs in the DED category, KOL specialists are cautious about the prospects for any treatment approach irrespective of how sound the supportive basic science behind the mechanism and specialists want to see a correlation to clinical data. The biggest concern with KOL's heading into Ph. 3 data is moving forward prior to establishing a stat sig signal in a proof of concept study. However, the KOLs noted the ophthalmology field has developed an improved understanding of the pathophysiology of DED and believe IL-1 plays an important role mediating important inflammatory factors of the disease and specialists believe there were many encouraging data pts in the earlier study

  - **Benefit on pain subset encouraging** – KOLs encouraged by benefit in subgroup, even thought not statistically significant. At least one KOL believed IL-1 blockade and pain relief make sense, noting IL-1 and IL-6 are both involved in nerve sensitization. Specialist thought targeting OSDI-pain was a good strategy

Source: MEDACorp Physician KOL calls

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# EBI-005 Market Assumptions

- **Market Size:** We assume a DED patient prevalence in the U.S. of ~5M, which is at the low end of the range of studies we could locate. We opted for the more conservative estimate based on (1) current script volumes suggest the low end of the range is more appropriate; (2) the AAO, American Academy of Ophthalmology, ests 5m adults age 50 or over suffer from DED

- **Segmentation:** We forecast ~20% of the prevalent pool seeks prescription anti-inflammatory medications (ex. Steroids) based on the current number of pts on Restasis. This translates to 1m patients, which we forecast will growth ~70% with the introduction of new medications to the market

- **EBI-005 market share:**
  - Base case - we forecast '005 will capture 20% (~400K patients) of the market, which assumes at least one other new market competitor

- **Duration of therapy**: We forecast '005 patients receiving ~3 prescriptions/patient/year, based on current usage ests for Restasis. If '005 demonstrates meaningful tolerability benefits in Ph. 3, then we forecast slightly higher uses rates of ~4 in our bull case.

- **Pricing & price increases**: We forecast '005 pricing using Restasis as a reference for likely pricing. Currently, Restasis is priced at an average selling cost of $330/script and we forecast that with price increases ASP will be ~$385 by the time '005 is commercially available

- **Exclusivity assumptions:** We forecast an '005 loss of exclusivity in 2034, based on composition and method of use patents. '005 is a biologic therapy and could see extended market exclusivity not factored into our ests

Source: Leerink research ests

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# We Forecast Significant Penetration into DED Market

| Dry Eye Model | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 | 2023 | 2024 | 2025 | 2026 | 2027 | 2028 | 2029 | 2030 | 2031 | 2032 | 2033 | 2034 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Prevalence of dry eye, US | 5.1 | 5.2 | 5.2 | 5.2 | 5.3 | 5.3 | 5.4 | 5.4 | 5.5 | 5.5 | 5.5 | 5.6 | 5.6 | 5.7 | 5.7 | 5.8 | 5.8 | 5.9 | 5.9 |
| % y/y growth | 0.8% | 0.8% | 0.8% | 0.8% | 0.8% | 0.8% | 0.8% | 0.8% | 0.8% | 0.8% | 0.8% | 0.8% | 0.8% | 0.8% | 0.8% | 0.8% | 0.8% | 0.8% | 0.8% |
| Treated with prescription Rx | 0.9 | 1.0 | 1.1 | 1.2 | 1.3 | 1.4 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.6 | 1.6 | 1.6 | 1.6 | 1.6 | 1.6 |
| % Rx treatment rate | 18% | 20% | 22% | 23% | 24% | 26% | 27% | 28% | 28% | 28% | 28% | 28% | 28% | 28% | 28% | 28% | 28% | 28% | 28% |
| **% share** | | | | | | | | | | | | | | | | | | | |
| Restasis (AGN) | 100% | 94% | 86% | 80% | 74% | 68% | 64% | 60% | 50% | 15% | 10% | 10% | 10% | 10% | 10% | 10% | 10% | 10% | 10% |
| Generics (Restasis, Lifitegrast) | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 10% | 45% | 50% | 50% | 50% | 50% | 65% | 65% | 65% | 65% | 65% |
| EBI-005 (EBIO) | 0% | 3.0% | 7% | 10% | 13% | 16% | 18% | 20% | 20% | 20% | 20% | 20% | 20% | 20% | 20% | 20% | 20% | 20% | 20% |
| Lifitegrast (SHPG) | 0% | 3.0% | 7.0% | 10% | 13% | 16% | 18% | 20% | 20% | 20% | 20% | 20% | 20% | 20% | 5% | 5% | 5% | 5% | 5% |
| total | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% |
| **Avg TRx per patient** | | | | | | | | | | | | | | | | | | | |
| Restasis (AGN) | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 |
| Generics (Restasis, Lifitegrast) | - | - | - | - | - | - | - | - | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 |
| EBI-005 (EBIO) | - | 3.0 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 |
| Lifitegrast (SHPG) | - | 3.0 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 |
| **Total TRx, MM** | | | | | | | | | | | | | | | | | | | |
| Restasis (AGN) | 3.2 | 3.3 | 3.3 | 3.2 | 3.2 | 3.1 | 3.1 | 3.0 | 2.5 | 0.8 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Generics (Restasis, Lifitegrast) | - | - | - | - | - | - | - | - | 0.5 | 2.3 | 2.6 | 2.6 | 2.6 | 2.7 | 3.5 | 3.5 | 3.5 | 3.6 | 3.6 |
| EBI-005 (EBIO) | - | 0.1 | 0.3 | 0.4 | 0.6 | 0.8 | 0.9 | 1.0 | 1.1 | 1.1 | 1.1 | 1.1 | 1.1 | 1.1 | 1.1 | 1.1 | 1.1 | 1.1 | 1.1 |
| Lifitegrast (SHPG) | - | 0.1 | 0.3 | 0.4 | 0.6 | 0.8 | 0.9 | 1.0 | 1.1 | 1.1 | 1.1 | 1.1 | 1.1 | 1.1 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 |
| **Net pricing** | | | | | | | | | | | | | | | | | | | |
| Restasis (AGN) | 369 | 387 | 406 | 427 | 452 | 479 | 508 | 539 | 555 | 572 | 589 | 589 | 589 | 589 | 589 | 589 | 589 | 589 | 589 |
| EBI-005 (EBIO) | - | 387 | 406 | 427 | 452 | 479 | 508 | 539 | 555 | 572 | 589 | 589 | 589 | 589 | 589 | 589 | 589 | 589 | 589 |
| Lifitegrast (SHPG) | - | 387 | 406 | 427 | 452 | 479 | 508 | 539 | 555 | 572 | 589 | 589 | 589 | 589 | 589 | 589 | 589 | 589 | 589 |
| **Net Sales** | | | | | | | | | | | | | | | | | | | |
| Restasis (AGN) | 1,172 | 1,281 | 1,325 | 1,387 | 1,452 | 1,506 | 1,595 | 1,624 | 1,405 | 438 | 303 | 305 | 308 | 310 | 313 | 315 | 318 | 320 | 323 |
| Generics (Restasis, Lifitegrast) | | | | | | | | | | | | | | | | | | | |
| EBI-005 (EBIO) | - | 36 | 112 | 180 | 265 | 367 | 465 | 562 | 583 | 605 | 628 | 634 | 639 | 644 | 649 | 654 | 659 | 665 | 670 |
| Lifitegrast (SHPG) | - | 36 | 112 | 180 | 265 | 367 | 465 | 562 | 583 | 605 | 628 | 634 | 639 | 644 | 162 | 164 | 165 | 166 | 167 |
| **Total Prescription market** | **1,172** | **1,354** | **1,548** | **1,746** | **1,981** | **2,241** | **2,525** | **2,747** | **2,571** | **1,648** | **1,560** | **1,572** | **1,585** | **1,598** | **1,124** | **1,133** | **1,142** | **1,151** | **1,160** |
| % y/y growth | 6% | 16% | 14% | 13% | 13% | 13% | 13% | 9% | -6% | -36% | -5% | 1% | 1% | 1% | -30% | 1% | 1% | 1% | 1% |

Source: Leerink Research estimates

# EBI-005 for Allergic Conjunctivitis (AC) Represents an Upside Driver If POC Data Are Positive

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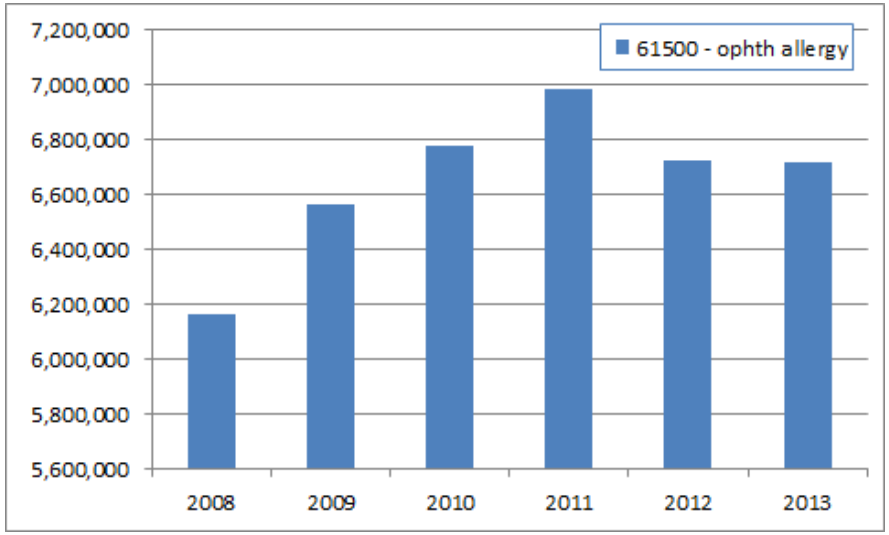
## Background

**Background**: AC is an inflammatory disease of the eye's conjunctiva, which is a membrane covering the inside of the eyelid and the white part of the eye. The condition is primarily a reaction to allergy-causing substances such as pollen or pet dander. The inflammation generally results in eye redness and symptoms of acute itching. Overall, epidemiology studies suggest a large percentage (15-40%) of Americans suffer from some form of AC. The more mild to moderate pts tend to get treated with antihistamine therapy or mast cell stabilizers (Patanol). EBIO is targeting the more severe forms of the AC population including AKC (atopic keratoconjunctivitis). AKC is more common and involves severe, chronic ocular inflammation associated with asthma/eczema and can afflict the patient for a prolonged period of their life. Treatment for these more severe forms of disease is limited to topical corticosteroids, which are unsatisfactory because they can increase the pts risk of glaucoma, cataracts and ocular infection

## Ph. 2 Proof of Concept ("POC")

EBIO plans to conduct a Ph. 2 trial of EBI-005 for treatment of AC in a randomized, controlled trial using controlled exposure models. The study is expected to include 145 subjects at a single center in Canada. Study subjects will be required to have a history of chronic ocular allergy and resistance to treatment with antihistamines and mast cell stabilizers. Patients will either be randomized to 5mg/mL of EBI-005 or vehicle. The primary endpoints will look at subjects in two different challenge models as assess the symptoms of AC as measured by ocular itching. The study will also study response of VKC populations and inform future development

## US Ophthalmic Allergy Meds – Annual TRx




*Source: IMS (USC code 61500)*

## Commercial Outlook

**We currently exclude AC sales from our model given the relatively early stage nature of the indication**

**However, the drug does have a promising mechanistic rational for treating AC and we would need to revisit our forecasts once proof of concept data are published in late 2014**

**Given the large market – positive data and a compelling product profile could serve as a meaningful catalyst for the stock**

**Using the low end of the prevalence range, we estimate that 30% penetration into the severe segment (est. 5-10% of total AC) of the market, at '005's projected pricing, could be worth $500 in sales. This may ultimately prove conservative if '005 is the only safe and effective treatment options for this subgroup of patients and pts were to get repeat dosing**

# EBIO P&L

**EBIO Annual P&L Summary (Adj. Basis)**
**EBIO Annual Product Summary**
(figures in $m, except per share data)

| | 2012A | 2013E | 1Q14E | 2Q14E | 3Q14E | 4Q14E | 2014E | 2015E | 2016E | 2017E | 2018E | 2019E | 2020E | 2021E | 2022E | 2023E | 2024E | 2025E | 2026 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EBI-005 (IL-1 blockade; dry eye disease) | - | - | - | - | - | - | - | - | - | 36 | 112 | 180 | 265 | 367 | 465 | 562 | 583 | 605 | 628 |
| EBI-005 (IL-1 blockade; allergic conjunctivitis) | | | - | - | - | - | | | | | | | | | | | | | |
| Collaboration revenue | - | 0.8 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| **Total Rev (MM)** | - | **0.8** | - | - | - | - | - | - | - | **36** | **112** | **180** | **265** | **367** | **465** | **562** | **583** | **605** | **628** |
| % y/y growth | *na* | *na* | *na* | *na* | *na* | *na* | *na* | *na* | *na* | *nm* | *208%* | *61%* | *47%* | *39%* | *27%* | *21%* | *4%* | *4%* | *4%* |
| COGS | - | - | - | - | - | - | - | - | - | 5 | 13 | 18 | 26 | 37 | 47 | 56.2 | 58.3 | 60.5 | 62.8 |
| % of sales | nm | 0% | *na* | *na* | *na* | *na* | nm | nm | nm | *15%* | *12%* | *10%* | *10%* | *10%* | *10%* | *10%* | *10%* | *10%* | *10%* |
| Gross Income | - | 0.8 | - | - | - | - | - | - | - | 31 | 98 | 162 | 238 | 331 | 419 | 505.4 | 524.7 | 544.8 | 565.6 |
| % of net sales | nm | 1 | | | | | nm | nm | nm | 85.0% | 88.0% | 90.0% | 90.0% | 90.0% | 90.0% | 90.0% | 90.0% | 90.0% | 90.0% |
| EBI-005 clinical development costs | 8.7 | 7.6 | 3.0 | 5.0 | 6.0 | 6.0 | 20.0 | 15.0 | 15.0 | 8.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 |
| Employee costs & other study costs | 6.6 | 6.5 | 1.6 | 1.7 | 1.5 | 1.7 | 6.5 | 6.5 | 6.8 | 7.2 | 7.5 | 7.9 | 8.3 | 8.7 | 9.1 | 9.6 | 10.1 | 10.6 | 11.1 |
| Other programs | - | - | | | | | - | - | - | 3.0 | 4.0 | 5.0 | 5.0 | 5.0 | 5.0 | 5.0 | 5.0 | 5.0 | 5.0 |
| Total R&D | 15.3 | 14.1 | 4.6 | 6.7 | 7.5 | 7.7 | 26.5 | 21.5 | 21.8 | 18.2 | 13.5 | 14.9 | 15.3 | 15.7 | 16.1 | 16.6 | 17.1 | 17.6 | 18.1 |
| % of sales | nm | nm | na | na | na | na | nm | nm | nm | *50%* | *12%* | *8%* | *6%* | *4%* | *3%* | *3%* | *3%* | *3%* | *3%* |
| G&A | 4.2 | 3.5 | 1.0 | 0.8 | 1.0 | 1.1 | 3.8 | 4.0 | 4.3 | 17.5 | 20.0 | 21.4 | 22.9 | 24.5 | 26.2 | 28.1 | 30.0 | 32.1 | 34.4 |
| % of sales | nm | 422% | na | na | na | na | nm | nm | nm | *48%* | *18%* | *12%* | *9%* | *7%* | *6%* | *5%* | *5%* | *5%* | *5%* |
| Sales reps cost | - | - | - | - | - | - | - | - | - | *25* | *26* | *28* | *29* | *30* | *32* | *34* | *35* | *37* | *39* |
| Marketing costs | - | - | - | - | - | - | - | - | - | *30* | *28* | *29* | *31* | *32* | *34* | *36* | *38* | *39* | *41* |
| Total S&M | - | - | - | - | - | - | - | - | - | 55 | 54 | 57 | 60 | 63 | 66 | 69 | 73 | 76 | 80 |
| Total operating expenses | 19.5 | 17.6 | 5.6 | 7.5 | 8.5 | 8.8 | 30.3 | 25.5 | 26.1 | 90.7 | 87.8 | 93.3 | 98.0 | 103.0 | 108.3 | 113.9 | 119.8 | 126.0 | 132.6 |
| **Operating (loss)/gain** | **(19.5)** | **(16.8)** | (5.6) | (7.5) | (8.5) | (8.8) | **(30.3)** | **(25.5)** | **(26.1)** | **(59.8)** | **10.6** | **68.5** | **140.1** | **227.7** | **310.4** | **391.5** | **404.9** | **418.8** | **433.0** |
| % of sales | nm | nm | na | na | na | na | nm | nm | nm | -164% | 10% | 38% | 53% | 62% | 67% | 70% | 69% | 69% | 69% |
| **Net financial expense** | (0.2) | (0.8) | (0) | (0) | (0) | 0 | (0.7) | (0.7) | (0.7) | (0.7) | 1.0 | 1.0 | 2.0 | 3.0 | 4.0 | 5.0 | 10.0 | 11.0 | 12.0 |
| **Pre-tax Income** | **(19.7)** | **(17.5)** | (6) | (8) | (9) | (9) | **(31.0)** | **(26.2)** | **(26.8)** | **(60.5)** | **11.6** | **69.5** | **142.1** | **230.7** | **314.4** | **396.5** | **414.9** | **429.8** | **445.0** |
| % Pre-tax Margin | nm | nm | *nm* | *nm* | *nm* | *nm* | nm | nm | nm | -166.3% | 10.4% | 38.7% | 53.7% | 62.8% | 67.6% | 70.6% | 71.2% | 71.0% | 70.8% |
| Taxes (benefit) | - | - | - | - | - | - | - | - | - | - | - | - | - | 81 | 110 | 139 | 145 | 150 | 156 |
| % Tax rate | *0.0%* | *0.0%* | - | - | - | - | *0.0%* | *0.0%* | *0.0%* | *0.0%* | *0.0%* | *0.0%* | *0.0%* | *35.0%* | *35.0%* | *35.0%* | *35.0%* | *35.0%* | *35.0%* |
| Preferred stock dividends | (3.1) | (3.6) | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| **Net Income/(loss) (MM)** | **(23)** | **(21)** | (6) | (8) | (9) | (9) | **(31)** | **(26)** | **(27)** | **(60)** | **12** | **70** | **142** | **150** | **204** | **258** | **270** | **279** | **289** |
| % of net sales | NM | NM | *N/M* | *N/M* | *N/M* | *N/M* | NM | nm | nm | -166.3% | 10.4% | 38.7% | 53.7% | 40.8% | 43.9% | 45.9% | 46.3% | 46.1% | 46.0% |
| **Basic & Diluted EPS** | **($0.50)** | **($0.39)** | **($0.36)** | **($0.48)** | **($0.56)** | **($0.56)** | **($1.96)** | **($1.44)** | **($1.45)** | **($2.89)** | **$0.54** | **$3.19** | **$6.39** | **$6.62** | **$8.84** | **$10.93** | **$11.21** | **$11.38** | **$11.56** |
| *Y/Y* | *NM* | *NM* | | | | | *NM* | *NM* | *NM* | *100%* | *-119%* | *486%* | *100%* | *3%* | *34%* | *24%* | *3%* | *2%* | *2%* |
| Weighted Avg Basic & Diluted Shares (MM) | 45.2 | 54.2 | 15.8 | 15.8 | 15.8 | 15.8 | 15.8 | 18.2 | 18.5 | 20.9 | 21.4 | 21.8 | 22.2 | 22.7 | 23.1 | 23.6 | 24.1 | 24.5 | 25.0 |
| % growth | NM | 20% | | | | | -71% | 15% | 2% | 13% | 2% | 2% | 2% | 2% | 2% | 2% | 2% | 2% | 2% |

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# EBIO Balance Sheet

| Balance Sheet | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Assets** | **2011A** | **2012A** | **2013E** | **2014E** | **2015E** | **2016E** | **2017E** | **2018E** |
| Cash/Equivalents | 0.7 | 7.9 | 0.2 | 25.3 | 50.8 | 25.7 | 16.9 | 30.4 |
| Prepaid expenses & other | 0.3 | 0.4 | 0.1 | - | - | - | - | - |
| **Total Current Assets** | **1.0** | **8.3** | **0.3** | **25.3** | **50.8** | **25.7** | **16.9** | **30.4** |
| Net Property, Plant & Equipment | 1.5 | 1.2 | 0.9 | 0.9 | 0.9 | 0.9 | 0.9 | 0.9 |
| Other | 0.1 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Total Long-Term Assets | 1.7 | 1.2 | 0.9 | 0.9 | 0.9 | 0.9 | 0.9 | 0.9 |
| **Total Assets** | **2.7** | **9.5** | **1.2** | **26.2** | **51.7** | **26.6** | **17.8** | **31.2** |
| **Liabilities & Shareholder's Equity** | | | | | | | | |
| Accounts payable | 1.1 | 1.1 | 0.7 | 0.9 | 0.9 | 0.9 | 0.9 | 0.9 |
| Accrued expenses | 0.6 | 0.5 | 0.3 | 0.4 | 0.3 | 0.2 | 0.1 | 0.1 |
| Equipment loan | 0.1 | 0.1 | 0.0 | - | - | - | - | - |
| Convertible notes payable | - | - | - | - | - | - | - | - |
| Notes payable, current portion | 0.5 | 0.1 | 1.6 | - | - | - | - | - |
| Other | - | - | - | - | - | - | - | - |
| **Total Current Liabilities** | **2.2** | **1.8** | **2.6** | **1.4** | **1.2** | **1.1** | **1.0** | **1.0** |
| Deferred revenue | - | - | 0.5 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 |
| Deferred rent | 0.1 | - | - | - | - | - | - | - |
| Restricted stock | 0.0 | 0.0 | - | - | - | - | - | - |
| Equipment loan | 0.1 | - | - | - | - | - | - | - |
| Notes payable | 0.3 | 1.8 | 3.3 | 3.3 | 3.3 | 3.3 | 3.3 | 3.3 |
| Warrant liability | 0.0 | 0.1 | - | - | - | - | - | - |
| Total Long-term Liabilities | 0.6 | 1.9 | 3.8 | 3.7 | 3.7 | 3.7 | 3.7 | 3.7 |
| **Total Liabilities** | **2.8** | **3.8** | **6.4** | **5.1** | **4.9** | **4.8** | **4.7** | **4.7** |
| **Total Shareholders' Equity** | **(0)** | **6** | **(5)** | **21** | **47** | **22** | **13** | **27** |
| **Total Liabilities & Shareholders' Equity** | **3** | **10** | **1** | **26** | **52** | **27** | **18** | **31** |

*Source: Company reports and Leerink estimates*

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# EBIO Statement of Cash Flows

| Reported Cash Flow | 2011A | 2012A | 2013E | 2014E | 2015E | 2016E | 2017E | 2018E |
|---|---|---|---|---|---|---|---|---|
| **Operating Activities** | | | | | | | | |
| GAAP Net Income | (12.8) | (19.7) | (18) | (31) | (26) | (27) | (60) | 12 |
| *Reconciliation items:* | | | | | | | | |
| Depreciation & amortization | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 |
| Non-cash Interest | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Change in fair value of warrant liability | (0.0) | 0.0 | - | - | - | - | - | - |
| Change in fair value of notes payable | - | - | - | - | - | - | - | - |
| Stock based compensation | 0.0 | 0.1 | 1.0 | 1.2 | 1.5 | 1.5 | 1.5 | 1.5 |
| Common stock issued for services | 0.0 | - | - | - | - | - | - | - |
| Decrease (Increase) in working capital | 1.5 | (0.1) | 2.1 | 1.2 | (0.1) | (0.1) | (0.1) | - |
| **Net Cash From Operations** | **(10.9)** | **(19.1)** | **(13.9)** | **(28.1)** | **(24.3)** | **(24.9)** | **(58.6)** | **13.6** |
| **Investing Activities** | | | | | | | | |
| Purchases of PP&E | (0.8) | (0.1) | (0.2) | (0.2) | (0.2) | (0.2) | (0.2) | (0.2) |
| **Net Investing Cash Flow** | **(0.8)** | **(0.1)** | **(0)** | **(0)** | **(0)** | **(0)** | **(0)** | **(0)** |
| **Financing Activities** | | | | | | | | |
| Proceeds from issuance of convertible | - | - | 3.5 | - | - | - | - | - |
| Proceeds from issuance of notes payable | - | 2.0 | 3.0 | - | - | - | - | - |
| Debt issuance costs | - | (0.1) | - | - | - | - | - | - |
| Payments on equipment financing | (0.6) | (1.0) | (0.1) | - | - | - | - | - |
| Proceeds from issuance of series A | 11.0 | 25.4 | - | - | - | - | - | - |
| Proceeds from issuance of common | 0.0 | - | - | 53.5 | 50.0 | - | 50.0 | - |
| Repurchase of unvested restricted stock | (0.0) | (0.0) | - | - | - | - | - | - |
| Proceeds from exercise of options | 0.0 | 0.0 | - | - | - | - | - | - |
| Other | - | - | - | - | - | - | - | - |
| **Net Financing Cash Flow** | **10.4** | **26.4** | **6.4** | **53.5** | **50.0** | - | **50.0** | - |
| Cash - Beginning Balance - Jan. 1st | 1.9 | 0.7 | 8 | 0 | 25 | 51 | 26 | 17 |
| Net Change in Cash | (1.2) | 7.2 | (8) | 25 | 25 | (25) | (9) | 13 |
| Cash - Ending Balance - Dec. 31st | 0.7 | 7.9 | 0 | 25 | 51 | 26 | 17 | 30 |

*Source: Company reports and Leerink estimates*

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# Near-Term Catalysts

**EBIO - Key Upcoming Events**

| Date (calendar period) | Event | Comments |
|---|---|---|
| Mid-2014 | Regulatory update: Competitor (to '005) lifitegrast to provide update on regulatory pathway forward | |
| Early 2014 | Initiation of first EBI-005 Phase III DED study | EBIO also plans to initiate 1-year safety trial in 2014 |
| May 4-8, 2014 | ARVO (Assoc. for Research in Vision & Ophthalmology) Annual Meeting for 2014 | Possible competitor data. Meeting will take place in Orlando |
| Oct. 18-21 | AAO (American Academy of Ophthalmology) 2014 Annual Meeting | Possible competitor data. Meeting will take place in Chicago |
| 2H14 | Possible Ph. 3 data for VRX's MIM-D3 (dry eye) | |
| 2H14 | Est. start of Ph. II proof-of-concept data for EBI-005 in allergic conj | |
| Early 2015 | Ph. III data first EBI-005 DED study | |
| Early 2015 | Est. start of second Ph. III study for EBI-005 in DED | EBIO stated in its S-1 that it may accelerate the timing of its second pivotal study |
| End of 2016 | Target BLA submission of EBI-005 | |

*Source: Company reports and Leerink estimates*

*Note: DED = dry eye disease*

# Disclosures Appendix

## Analyst Certification

I, Jason M. Gerberry, JD, certify that the views expressed in this report accurately reflect my views and that no part of my compensation was, is, or will be directly related to the specific recommendation or views contained in this report.

| Distribution of Ratings/Investment Banking Services (IB) as of 12/31/13 | | | | |
|---|---|---|---|---|
| | | | IB Serv./Past 12 Mos. | |
| Rating | Count | Percent | Count | Percent |
| BUY [OP] | 118 | 64.50 | 30 | 25.00 |
| HOLD [MP] | 65 | 35.50 | 2 | 3.00 |
| SELL [UP] | 0 | 0.00 | 0 | 0.00 |

## Explanation of Ratings

**Outperform (Buy):** We expect this stock to outperform its benchmark over the next 12 months.

**Market Perform (Hold/Neutral):** We expect this stock to perform in line with its benchmark over the next 12 months.

**Underperform (Sell):** We expect this stock to underperform its benchmark over the next 12 months.The degree of outperformance or underperformance required to warrant an Outperform or an Underperform rating should be commensurate with the risk profile of the company.

For the purposes of these definitions the relevant benchmark will be the S&P 600® Health Care Index for issuers with a market capitalization of less than $2 billion and the S&P 500® Health Care Index for issuers with a market capitalization over $2 billion.

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