# Eleven Biotherapeutics

Equity Research

Company Quick Take

November 13, 2014

**Price: $11.24** (11/12/2014)

**Price Target: $35.00**

**OUTPERFORM (1)**

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**Key Data**

| | |
|---|---|
| Symbol | NASDAQ: EBIO |
| Market Cap (MM) | $182.9 |

## *EBI-005 On Track For Pivotal Dry Eye Readout In Q2:2015*

### The Cowen Insight

Eleven reported Q3 earnings and reported that the pivotal Phase III dry eye study for EBI-005 has completed enrollment and is on track for a Q2:15 data readout. Additionally, we continue to believe that little-to-no value is being ascribed to the AC indication, which reported positive data last month. Given this and our consultants' views on the dry eye program, we would be buying here.

### Pivotal Dry Eye Study Fully Enrolled

Eleven Biotherapeutics reported Q3 earnings and provided updates on the company's clinical development programs. Importantly, the pivotal Phase III dry eye disease program for EBI-005 (topical IL-1 inhibitor) has completed enrollment and is expected to report topline results in Q2:15. Last month, Eleven also reported positive Phase II results for EBI-005 for allergic conjunctivitis and next steps for the additional indication are expected in early 2015. Regarding dry eye, the Phase III OASIS study is being conducted at over 40 U.S. sites with a total enrollment of 669 patients. At this time, over half of the enrolled patients have already completed the study. Eleven's initial positive data, and thoughtful and meticulous approach for the design of the dry eye pivotal trial continues to provide us – and our consultants – with optimism towards the probability of success. Moreover, physicians continue to assert that the scientific rationale behind EBI-005 and Eleven's other programs remain sound and that the new ocular pain symptoms endpoint for the dry eye program is very relevant (commercially/clinically) to the disease. We would reiterate that our consultants continue to indicate that Restasis is a fairly poor treatment given its efficacy and tolerability profile. Nonetheless, it is the market leader and the only approved dry eye drug with roughly $1B in sales. Our consultants stress that a "better" therapeutic option could expand dry eye prescription utilization by 3-4x the current Restasis use, making the prescription target market likely actually closer to $3-4B. Most importantly, given the profile, they indicate that EBI-005 would be an exceedingly welcome addition to the treatment paradigm. Our model has "peak" sales of roughly $500MM, but we believe this is clearly a conservative number if the initial clinical profile holds up when results are reported in the second quarter of next year. Stated another way, there is no reason why EBI-005 couldn't be a $1B+ drug, in our view.

As for the specifics of the EBI-005 pivotal dry eye trial, the study has two arms, with patients being treated with either EBI-005 or vehicle-control for 12 weeks followed by a 3-week safety assessment. Of note, Eleven is using strict inclusion criteria for enrollment as patients must have moderate to severe dry eye and exhibit both signs and symptoms of the condition. This is critical since the study – similar to other dry eye registration studies – has sign and symptoms co-primary endpoints. For these endpoints, Eleven is measuring the change in total corneal fluorescein staining score (a sign of dry eye) and the improvement in ocular pain and discomfort (a symptom of dry eye). Furthermore, the company has taken extensive measures to select sites that are well-experienced running dry eye trials and are also providing comprehensive training for physicians prior to and during the trial. Eleven has elected to not allow

any use of artificial tears during the study as it is a well-known confounder of dry eye clinical trials and EBI-005 patients in Phase II reported significantly less use. Patients in both arms will be asked if they have used tears at every physician visit and any utilization will be recorded and provided as part of the complete data set.

A separate 12-month safety study required for the EBI-005 dry eye BLA submission will also begin by year-end. Finally, the company was also granted a new composition-of-matter/methods of use patent for EBI-005 with an expiration of 2031.

### The Valuation Is Attractive Here

Assuming clinical and commercial success for EBI-005 (while excluding any potential other pipeline assets, including the AC indication for EBI-005) we arrive at a base valuation of $35 per share. This assumes that Eleven takes the product to market via their own sales force in 2017, and that by year 5 of the launch EBI-005 has reached $500MM+ in sales. Alternatively, a potential acquirer with its own commercial infrastructure – which would significantly lower our spending assumptions in the DCF – would argue for a valuation of the EBI-005 opportunity alone of $50-55. Given the approaching data readouts and our belief in the likelihood of clinical success, and the potential commercial outcomes, we would be adding at these levels.

### Shire Filing Disclosure Indicates That The Dry Eye Regulatory Environment Is Improving

In our EBIO initiation in early March, we discussed at length the historically difficult dry eye disease regulatory environment, which is centered around the requirement of meeting two potentially non-correlated co-primary endpoints (signs and symptoms). However, we also noted how that environment has been easing/improving in recent years with what appears to be a more amenable FDA. Examples of this have been the emergence of the "totality of the data" thesis and the FDA's willingness to allow Shire to explore a novel, more simplistic and straightforward, patient-reported eye dryness symptoms endpoint (as opposed to the more complicated tradition OSDI measurement). Additionally, it appears the Agency may be amenable to allowing positive Phase III results for the signs and symptoms endpoints in separate Phase III studies (which is discussed in our note here). This is also supported by Shire's decision to file the Lifitegrast NDA in Q1:2015. The bottom line is that it appears that the Agency is considering a more pragmatic pathway and the regulatory environment is improving. Ultimately, we believe this bodes well for Eleven Biotherapeutics' Phase III EBI-005 dry eye program.

### The Industry Standard CAPT Model Now Identified As Appropriate For Measuring The Late-Phase Allergic Response

Last month, Eleven reported results from EBI-005's (topical IL-1 inhibitor) Phase II program in allergic conjunctivitis. The Phase II program consisted of two studies, employing two distinct models with 6 allergen challenges over 2.5 weeks, in moderate to severe allergic conjunctivitis patients: (1) a modified conjunctival allergen provocation test (CAPT); and (2) a modified environmental exposure chamber (EEC) model. The main endpoint, the mean change from baseline in patient-reported ocular itching compared to vehicle control, was statistically significant in the CAPT model, but not in the EEC model. While these results initially appear mixed, Eleven was exceedingly clear going into the data that both models were being evaluated to identify an appropriate model/pathway for late-phase ocular allergy response to take forward to Phase III and that significant optionality exists as we previously wrote here. Therefore, while the EEC study was not successful, the successful CAPT study results will be used to forge a pathway forward – and we will likely learn of that pathway in early 2015 after the company meets with the FDA. Furthermore, we are comforted by the fact that the CAPT model – which was employed in the successful

study and will most likely be used going forward – is the model that the majority of approved ocular therapeutic agents have used for registration studies. Ultimately, this data suggests that EBI-005 could be a potentially useful treatment option for later-stage moderate to severe patients who currently have a lack of effective treatment options available. Many of these patients have to resort to steroid treatment, which is commonly associated with significant side effects. The bottom line is that we continue to believe that very little-to-no valuation is being ascribed to the allergic conjunctivitis indication, which we believe is overly conservative when this program has potential to advance into Phase III within the next year.

### Specifics Of The EBI-005 Phase II Allergic Conjunctivitis Results

As noted above, while the study employing the EEC model (~100 patients; 50 per arm, treatment and placebo) did not achieve statistical significance on its endpoints, the study using the CAPT model (~50 patients; 25 per arm, treatment and placebo) did. A 5mg/mL EBI-005 dose was used and the most important endpoint of ocular itching achieved statistical significance at the second to last ($p=0.033$) and the final – ($p=0.045$) assessment time points. The final assessment time point was pre-specified. We would note that achieving statistical significance in such a small study is impressive. Looking ahead, potential registration studies could be 200 patients or more, which would further increased the powering and probability of a statistically significant outcome.

Other exploratory endpoints in the CAPT study of ocular tearing (second to last, $p=0.027$; final, $p=0.044$) and associated nasal symptoms (second to last, $p=0.004$; final, $p=0.011$) were also statistically significant. These were not met in the EEC study. Overall, 27% of subjects reported a mild adverse event and the safety and tolerability of EBI-005 compared to vehicle control was balanced, with no treatment-related serious adverse events and no immunogenicity. The final results will be submitted at an upcoming ophthalmology conference.

## Figure 1 EBI-005 Dry Eye Market Build

| ESTIMATED U.S. DRY EYE TREATMENT MARKET | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2012 | 2013 | 2014E | 2015E | 2016E | 2017E | 2018E | 2019E | 2020E | CGR | Comments |
| **Restasis U.S. Penetration Of Est Dry Eye Market (AGN)** | 80% | 80% | 80% | 78% | 74% | 67% | 62% | 56% | 51% | | - Leading treatment - market creator |
| Estimated Patients ('000) | 1,825 | 2,070 | 2,180 | 2,185 | 2,190 | 2,120 | 2,080 | 2,010 | 1,975 | | - Generics may not come upon market expiry; poor compliance |
| Average Price Per Year Due To Low Utilization | $685 | $720 | $765 | $805 | $845 | $885 | $930 | $975 | $1,025 | | - ~5% annual price increases |
| Annual Prescriptions ('000) | 2,820 | 2,955 | $3,112 | $3,119 | $3,126 | $3,026 | $2,969 | $2,869 | $2,819 | | |
| Estimated Sales U.S. ($MM) | $750 | $895 | $1,000 | $1,055 | $1,110 | $1,125 | $1,160 | $1,175 | $1,215 | +6% | - US sales dominate |
| **Lifitegrast U.S. Penetration Of Est Dry Eye Market (SHPG)** | | | | 4% | 8% | 13% | 16% | 20% | 22% | | - First treatment to address symptoms of dry eye |
| Patients ('000) | | | | 39 | 89 | 159 | 205 | 266 | 323 | | - Compliance should be better than Restasis due to efficacy |
| Average Price Per Year | | | | $1,610 | $1,690 | $1,770 | $1,860 | $1,950 | $2,050 | | - Priced at a premium to Restasis; and higher utlization |
| Annual Prescriptions ('000) | | | | 46 | 106 | 189 | 244 | 316 | 384 | | |
| Estimated Sales U.S. ($MM) | | | | $50 | $120 | $225 | $305 | $415 | $530 | | - Expected to rapidly gain market share |
| **EBI-005 U.S. Penetration Of Est Dry Eye Market** | | | | | | | 4% | 8% | 10% | | - Second player to reach market that treats symptoms effectively |
| Patients ('000) | | | | | | | 81 | 144 | 186 | | - Potential 2018 U.S. market launch |
| Average Price Per Year | | | | | | | $1,860 | $1,950 | $2,050 | | - Pricing in-line with Lifitegrast |
| Annual Prescriptions ('000) | | | | | | | 96 | 172 | 221 | | |
| **Estimated Sales U.S. ($MM)** | | | | | | **$50** | **$120** | **$225** | **$305** | | - Strong launch anticipated in exceedingly large market |
| Steroids/Tears/Others U.S. Estimated Penetration Of Dry Eye Market | 21% | 20% | 20% | 19% | 18% | 17% | 15% | 14% | 13% | | - Use declines with the entrance of new, more effective products |
| Patients ('000) | 1,510 | 1,630 | 1,740 | 1,735 | 1,765 | 1,730 | 1,695 | 1,665 | 1,640 | | - Compliance low and similar to Restasis; short duration of treatment |
| Average Price Per Year | $215 | $225 | $235 | $245 | $255 | $270 | $285 | $300 | $315 | | - Mainly generic or low priced products |
| Estimated Sales U.S. ($MM) | $195 | $220 | $245 | $255 | $270 | $280 | $290 | $300 | $310 | +6% | - Use remains steady |
| **Total U.S. Dry Eye Market Sales (MM)** | **$945** | **$1,115** | **$1,245** | **$1,360** | **$1,500** | **$1,680** | **$1,875** | **$2,115** | **$2,360** | **+12%** | - Larger % of market penetrated due to multiple treatment options |
| **% Growth** | **+15%** | **+18%** | **+12%** | **+9%** | **+10%** | **+12%** | **+12%** | **+13%** | **+12%** | | - Growth should be rapid given new, more effective drugs |

Source: Cowen and Company; PriceRx

# *Valuation Methodology And Risks*

## Valuation Methodology

### Pharmaceuticals/Specialty

For our valuation methodology, we arrive at fair value utilizing a discounted cash flow (DCF) approach to derive our 12-month price target.

## Investment Risks

### Pharmaceuticals/Specialty

**Risks include:** (1) growing competitive dynamics in the specialty pharmaceuticals space; (2) the ability of management to execute on external growth by successfully acquiring new strategic, accretive products; (3) the ability to grow organically and keep the product pipeline robust; (4) potential regulatory delays, rejections, or failures of pipeline products; (5) economic sensitivity of any self-pay products or weakening consumer demand; (6) domestic or international pricing pressures for marketed products; and (7) failure to execute on new product launches.

## Risks To The Price Target

Eleven is a development-stage specialty pharmaceutical company and with that carries risk. Failure to successfully develop EBI-005 could result in a significant decrease to our valuation.

# Addendum

## Stocks Mentioned In Important Disclosures

| Ticker | Company Name |
|---|---|
| EBIO | Eleven Biotherapeutics |

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**Outperform (1):** The stock is expected to achieve a total positive return of at least 15% over the next 12 months

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**Assumption:** The expected total return calculation includes anticipated dividend yield

***Cowen and Company Rating System until May 25, 2013***

**Outperform (1):** Stock expected to outperform the S&P 500

**Neutral (2):** Stock expected to perform in line with the S&P 500

**Underperform (3):** Stock expected to underperform the S&P 500

**Assumptions:** Time horizon is 12 months; S&P 500 is flat over forecast period

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|---|---|---|---|---|
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| Hold (b) | 278 | 37.87% | 10 | 3.60% |
| Sell (c) | 16 | 2.18% | 0 | 0.00% |

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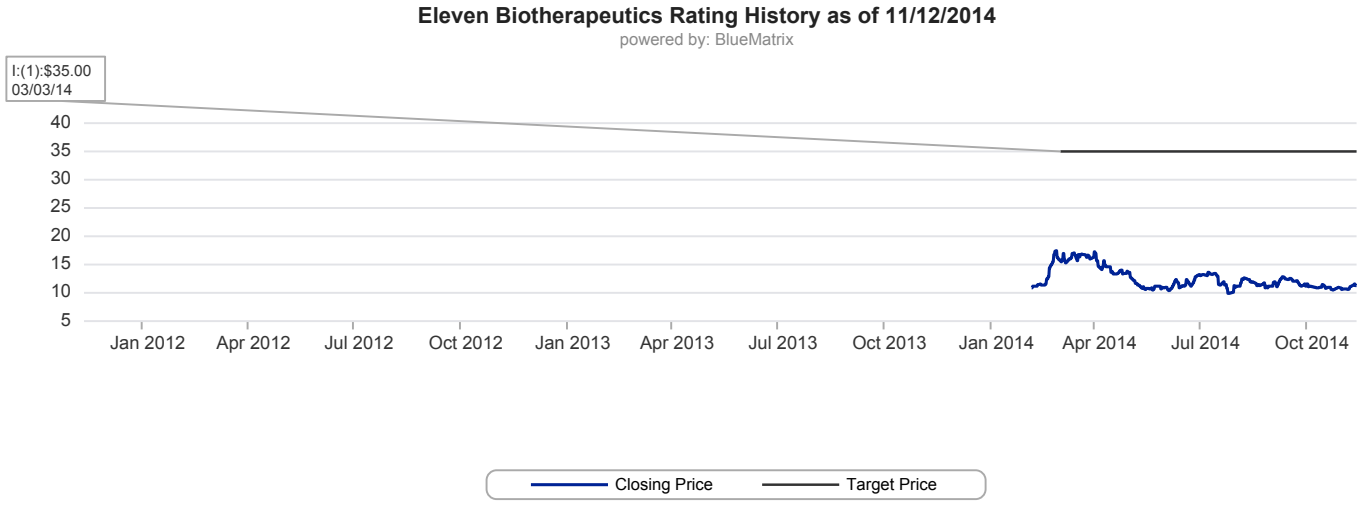


**Legend for Price Chart:**

I = Initiation | 1 = Outperform | 2 = Market Perform | 3 = Underperform | UR = Price Target Under Review | T = Terminated Coverage | $xx = Price Target | NA = Not Available | S=Suspended

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