Zacks Small-Cap Research

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# AntriaBio, Inc. (ANTB-OTC)

## *ANTB: Preclinical Data at ADA Supports Development of AB101*

| | |
|---|---|
| **Current Recommendation** | **Hold** |
| Prior Recommendation | N/A |
| Date of Last Change | 10/07/2014 |
| Current Price (08/17/15) | $1.60 |
| **Target Price** | **$2.25** |

**Update**

AntriaBio, Inc. recently presented encouraging pre-clinical data at the ADA conference on its lead compound, AB101 - the first once-weekly basal insulin. The data showed AB101 drug substance had comparable in vitro pharmacology to native insulin and displayed an extended subcutaneous insulin absorption profile in two different animal species, leading to slow onset, peak-less and sustained insulin levels with corresponding reductions in glucose levels.

We believe that AntriaBio remains on track to file the U.S. IND in the third quarter of calendar year 2015. We see the current valuation fair at $2.25 per share and maintain our 'Hold' rating.

## SUMMARY DATA

| | |
|---|---|
| **52-Week High** | **$2.25** |
| **52-Week Low** | **$0.90** |
| **One-Year Return (%)** | **-7.51** |
| **Beta** | **-1.79** |
| **Average Daily Volume (sh)** | **9,029** |
| **Shares Outstanding (mil)** | **24** |
| **Market Capitalization ($mil)** | **$39** |
| **Short Interest Ratio (days)** | **N/A** |
| **Institutional Ownership (%)** | **0** |
| **Insider Ownership (%)** | **35** |
| **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 2015 Estimate** | **N/A** |
| **P/E using 2016 Estimate** | **N/A** |

| | |
|---|---|
| **Risk Level** | **Above Average** |
| **Type of Stock** | **Small-Growth** |
| **Industry** | **Med-Biomed/Gene** |

## ZACKS ESTIMATES

**Revenue**
(In millions of $)

| | Q1 (Sep) | Q2 (Dec) | Q3 (Mar) | Q4 (Jun) | Year (Jun) |
|---|---|---|---|---|---|
| 2014 | 0 A | 0 A | 0 A | 0 A | 0 A |
| 2015 | 0 A | 0 A | 0 A | 0 E | 0 E |
| 2016 | | | | | 0 E |
| 2017 | | | | | 0 E |

**Earnings per Share**
(EPS is operating earnings before non-recurring items)

| | Q1 (Sep) | Q2 (Dec) | Q3 (Mar) | Q4 (Jun) | Year (Jun) |
|---|---|---|---|---|---|
| 2014 | -$0.12 A | -$0.27 A | -$0.76 A | -$0.11 A | -$1.04 A |
| 2015 | -$0.12 A | -$0.16 A | -$0.14 A | -$0.19 E | -$0.62 E |
| 2016 | | | | | -$0.61 E |
| 2017 | | | | | -$0.64 E |

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## WHAT'S NEW

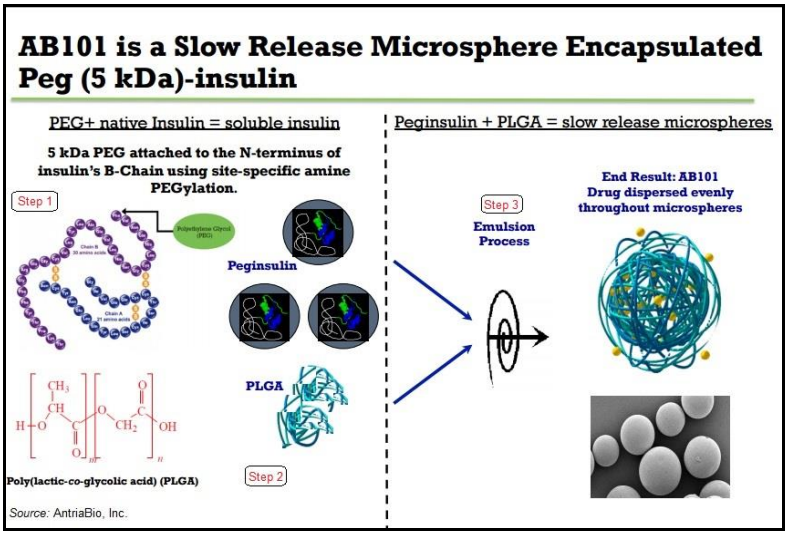
On June 8, 2015, AntriaBio (ANTB) announced preclinical results for its once-weekly basal insulin candidate, AB101, in a presentation titled "*The in Vitro and in Vivo Pharmacology of AB101, a Potential Once-Weekly Basal Subcutaneous Insulin*" at the American Diabetes Association 75th Scientific Sessions® in Boston, MA. The data support our belief that AB101 will be the first once-weekly basal insulin product. We expect that AntriaBio is on track to file the U.S. IND in the third quarter of calendar year 2015.

**AntriaBio's AB101 – The First Once-Weekly Basal Insulin**

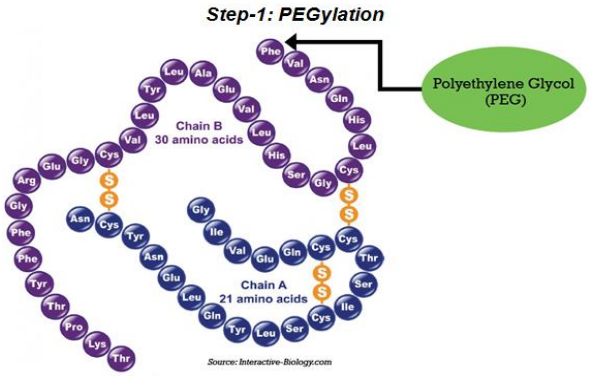
AntriaBio is developing AB101, a product that aims to be the first once-weekly basal insulin. AB101 is a formulation of human recombinant insulin (non-analog) for subcutaneous injection that is designed to release insulin slowly and uniformly over a period of approximately one week without an adverse initial burst. AB101 is a proprietary formulation developed by the company to preserve the integrity and biological activity of insulin through the manufacturing process. Despite the once-weekly dosing regimen, the dose of AB101 can be administered in an acceptable volume through a relatively small (narrow gauge) needle. AB101 was engineered to provide desired release kinetics using a common biodegradable material called PLGA or poly(lactic-co-glycolic acid). PLGA biodegrades through a very predictable and consistent hydrolysis, eliminating an initial undesirable burst of insulin release. With these characteristics, AB101 should provide high quality basal insulin for the majority of insulin-dependent diabetics without significant injection site reaction or burst of serum insulin levels.

- ***How Is AB101 Made?***

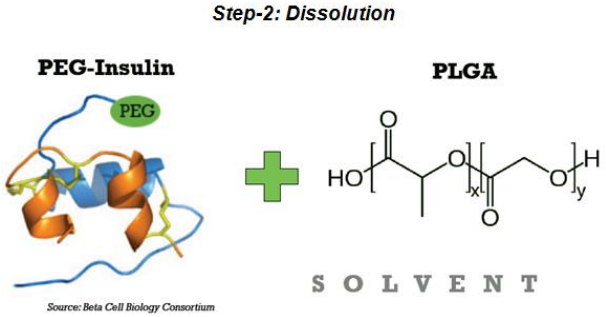
AntriaBio is not the first company to attempt to develop a once-weekly basal insulin injection. Many have failed in formulation work prior to AntriaBio's AB101. There are essentially two strategies to develop a weekly basal insulin injection, either formulate with polyethylene glycol (PEG) or encapsulate in PLGA or polyglutamate (pGlu) microspheres.



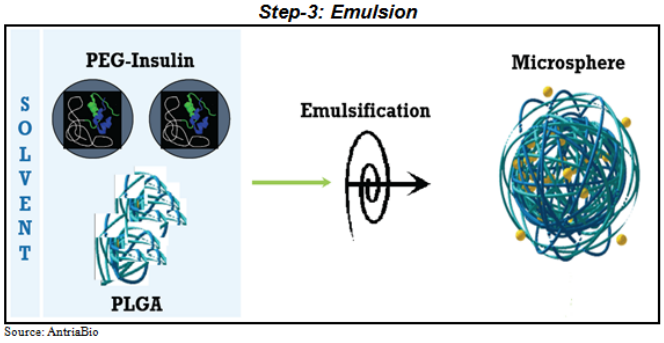

**Step-1: PEGylation:** Formulation with PEG has been a well-documented strategy for improving half-life and extending duration of action. PEGylation is known to enhance protein stability and solubility, reducing dosing frequency, and enhancing plasma circulation. Numerous pharmaceutical products have been attached to PEG, including granulocyte colony-stimulating factor (Amgen's Neulasta), certolizumab (UCB's Cimzia), anti-VEGF aptamer (Pfizer's Macugen), alpha-interferon (Merck's PEGintron, Roche's Pegasys), adenosine deaminase (Enzon's Adagen), and uricase (Savient's Pegloticase), to name a few.




**Step-2: Dissolution:** Dissolving PEG-insulin with a polymer such as PLGA is a strategy designed to facilitate delivery of dose and allow extended release of the PEG-insulin into the body by hydrolysis. Dissolution of PLGA allows a slow release of the PEG-insulin at a controlled rate designed by AntriaBio scientists based on the monomers used in the formulation.




**Step-3: Emulsion:** After the PEG-Insulin and PLGA are dissolved in a solvent the mixture is put through an emulsification process to create uniform, monolithic microspheres. After the solution is delivered the microspheres are degraded by hydrolysis at a uniform and controlled rate, releasing the PEG-insulin into circulation.



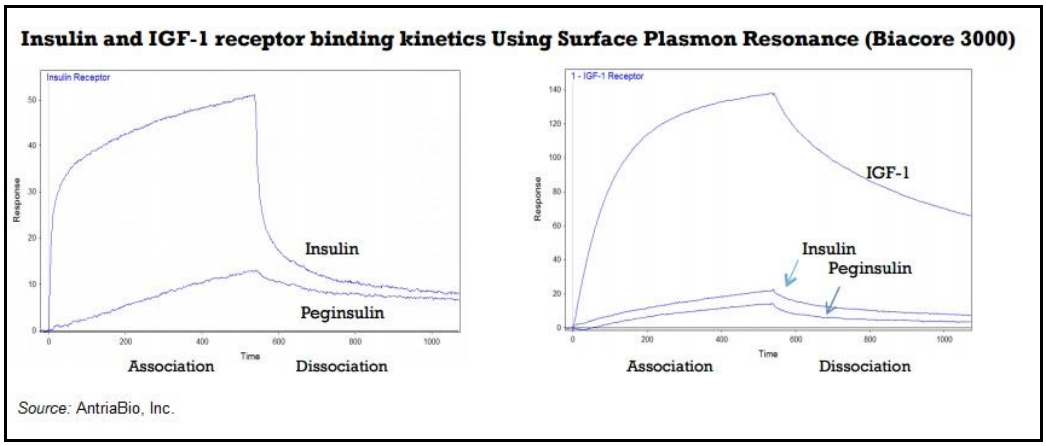

## AB101 Preclinical Proof of Concept Pharmacology Studies

The results from the preclinical proof of concept pharmacology studies showed that AB101 has comparable in vitro pharmacology to native insulin, and in two animal species (rats and dogs) displayed an extended subcutaneous insulin absorption profile, leading to slow onset, peakless and sustained insulin levels with corresponding reductions in glucose levels, without acute hypoglycemia caused by an initial insulin burst. As per management, these observations occurred at clinically relevant dose projections, demonstrating proof of concept of the potential for AB101 as a weekly subcutaneous basal insulin therapy in patients with diabetes mellitus.

- ***Looking at Receptor Binding Studies***

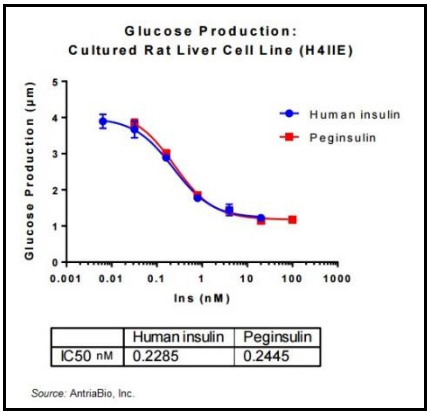
Receptor binding studies showed that the AB101 drug substance (referred to as “Peginsulin” in the graphs below) was found to have both receptor binding affinity for the insulin receptor and receptor-mediated biological activity that was similar to native insulin. Additionally, the AB101 drug substance displayed low affinity for the IGF-1 receptor,

which indicates a low mitogenic (relating to mitosis or cell division) potential. We see this low risk of mitogenicity as good news since altering the structure of insulin molecules has been known to not only significantly change its activity, but can also lead to deleterious health effects (Zib *et. al*, 2006). AB101 requires no modification to the native recombinant insulin structure, and thus a lower risk of mitogenicity. Management believes that these results should predict insulin activity in humans. We are hopeful that similar results are seen in the future Phase 1 and 2 trials in human subjects.




➢ ***Looking at Glucose Production in Rat Liver Cells***

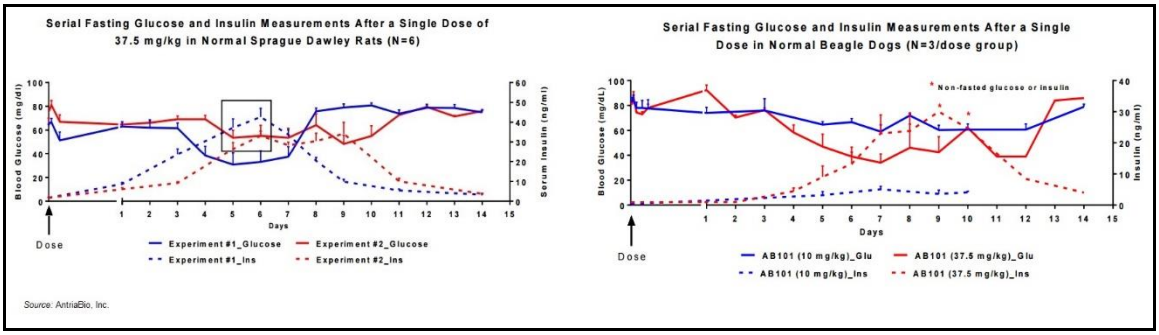
The AB101 drug substance (referred to as "Peginsulin" in the graph below) inhibited glucose production in rat liver cells with the same potency and to the same magnitude as native insulin. The inhibitory effect on glucose production by the drug substance occurred at an $IC_{50}$ of 0.24 nM, which was close to that of native insulin at an $IC_{50}$ of 0.23 nM. In our opinion, the predictable and similar effect on glucose production by the drug substance supports moving forward with AB101.

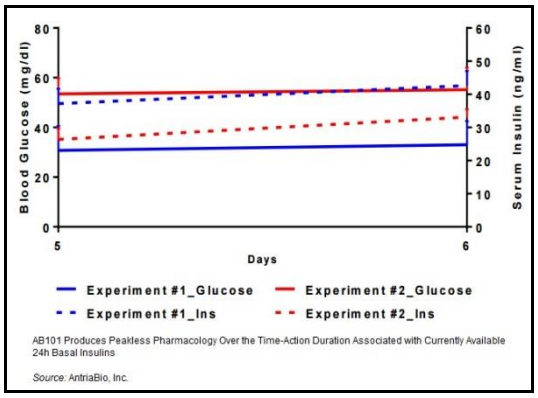



➢ ***Looking at in Vivo Studies in Rats & Dogs***

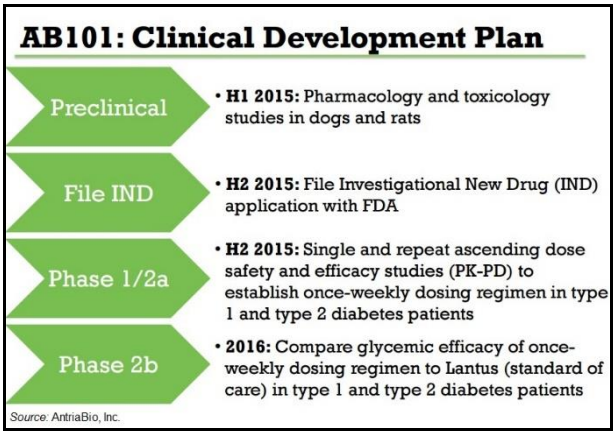
In vivo studies were conducted in both rats and dogs, and both fasting insulin as well as glucose levels were measured at baseline and several times over a two week period after a single dose subcutaneous administration of AB101 (37.5 mg/kg or vehicle control in rats [n=6/group]; 10 mg/kg or 37.5 mg/kg in dogs [n=3/group]).

In both the rat and dog species, the single dose administration of AB101 led to slow onset, peakless and sustained increases in insulin, with a Cmax of > 30 ng/mL at 7 - 9 days post dose, with corresponding glucose reductions by 30% to 50% over the course of the week. The ratio of $AUC_{(0\text{-}24h)}$ to $AUC_{(0\text{-}total)}$ for insulin and glucose was < 1%, and a similar sustained PK/PD profile was seen in a diabetic animal model. We see these results as encouraging, with no initial undesirable effects of insulin bursts or hypoglycemia.




**The AB101 Clinical Development Plan**




The near-term clinical development plan with AB101 consists of:

1. Complete the build-out of the manufacturing facility in Louisville, CO and produce AB101 material in accordance with current good manufacturing practices (cGMP). We are still expecting this to be completed by August 2015.

2. File U.S. IND

As per management, IND-enabling work is ongoing, and an IND application for clinical trials is forthcoming. We continue to believe that AntriaBio is still on track to file the U.S. IND with the FDA in the third quarter 2015. AntriaBio believes that AB101 will likely qualify as a new molecular entity (NME) for listing in the U.S. FDA's Orange Book. However, because the company plans to reference significant historical information on insulin, PEGylation, dissolution, and emulsification, management believes the regulatory hurdle may be more favorable, including the low likelihood the company would have to conduct a dedicated cardiovascular (CV) outcomes study to gain approval or marketing rights. AntriaBio believes the AB101 intellectual property will be protected by existing patents around the PEG attachment to insulin and the mixture of the PEG-insulin with PLGA that do not expire until 2024. New patents have been filed around the manufacturing process that would likely protect AB101 until 2034 based on priority date.

3. Initiate Phase 1 clinical study in the U.S.

The objectives of the first clinical study will be to assess the single dose of AB101 in Type-1 and Type 2 diabetes patients currently using Sanofi's Lantus. This will be an in-hospital stay where roughly 40-50 patients will come in stable on Lantus and transitioned to receive one dose of AB101 and then monitored continuously for the next week. We believe results will be pretty cut-and-dry with respect to the utility of AB101. If a patient can effectively transition from daily Lantus to once-weekly AB101 with no issues over the following week in terms of glucose control and safety/tolerability, AntriaBio has a blockbuster on its hands. If there are significant issues in terms of patients experiencing hypo- or hyperglycemia or severe adverse events, then AntriaBio needs to go back to the drawing board with respect to the formulation of AB101. Management believes the first study for AB101 should commence in the fourth quarter of 2015. This will likely be in Type 1 diabetics, but we will have a better sense of the exact timing of this first study to begin once the IND has been filed. We believe the initial Phase 1 studies should complete by the middle of calendar 2016.

4. Move into Phase 2 clinical studies in the U.S.

Following successful completion of the Phase 1 clinical studies noted above, Phase 2 trials should begin in both Type-1 and Type-2 diabetics. These will primarily be longer-duration safety and tolerability studies, with accepted biomarkers for glucose efficacy (i.e. HbA1c) comparing AB101 to a standard of care basal insulin such as Sanofi's Lantus (glargine). If the proof of concept trials are successful, we expect the company to expand the clinical program to include Phase 3 registration trials in various regions around the world, including the U.S. and Europe.

Ultimately, we expect AntriaBio to look to partner AB101 with a larger pharmaceutical company with a heavy presence in the diabetes market, such as Novo Nordisk, Sanofi, and Eli Lilly. Other major players include Merck, Bristol-Myers, Roche, Novartis, Boehringer Ingelheim, and AstraZeneca. However, to get to the point where partnering AB101 is feasible, we believe the company will need to complete through Phase 2 clinical testing in the U.S. The goal is to show endpoints of glycemic control and safety comparable to a product like Lantus. We believe data from the first clinical study can be generated by the middle of 2016. We believe this study will cost an estimated $4 million all-in for AntriaBio.

**Conclusion**

Upon reviewing the preclinical proof of concept pharmacology data, we continue to remain optimistic regarding the AB101 story. In our opinion, it was very reassuring to see that no acute undesirable insulin bursts or glucose reductions were observed. Furthermore, we believe that the slow onset, sustained insulin increases with corresponding glucose reductions over the course of about one week in both the dog and rat species support a once-weekly dosing of basal insulin for patients with diabetes. Obviously, it is still early on in the process, but we view these results as encouraging. We are hopeful that the efficacious doses used in the animal models will be readily translated to human clinically relevant doses and dose volumes. Management believes that the inter-species homology of insulin/receptor predicts insulin activity in humans, and we are hoping, that in the future, results from human trials show this predictable pattern. At this point, we continue to view AB101 as a promising new insulin therapy option for individuals with diabetes as well as clinicians. The preclinical data shows that the once-weekly injection offers a reproducible, slow and sustained release of insulin and reduction in glucose over the intended weekly dosing period, which if translated to patients with diabetes should provide uniform glycemic control with the convenience and compliance of a once-weekly injection and a lower risk of hyperglycemia.

We continue to believe AB101 has peak sales in the area of $3.5 billion by 2027. Only investors today certainly do not need to wait around to 2027 to see shares of AntriaBio move higher. In fact, we believe there are a number of value-creating inflection points on the horizon over the next two years, culminating with the signing of a major development and commercialization partnership for AB101 in late 2016 after the Phase 1/2 data has been generated. As noted above, we expect the results of the Phase 1 proof-of-concept study to be pretty cut-and-dry. Either AB101 works or it does not. If it works, AB101 could see a ten-fold increase in valuation as big pharmaceutical companies like Sanofi, Novo Nordisk and Eli Lilly, now become interested in acquiring the company. It's also important to mention that AntriaBio plans on announcing one or two additional pipeline candidates this year in the metabolic space, building off of proof-of-concept work for AB101.

Based on historical "big pharma / small-biotech" take-outs, we believe a deal will get done prior to the initiation of the pivotal registration program in 2017. We believe a company like Sanofi or Eli Lilly would be quite comfortable paying a handsome premium to acquire AB101 if their internal numbers agree with our modeling that peak sales are in the $3.5 billion range by 2027.

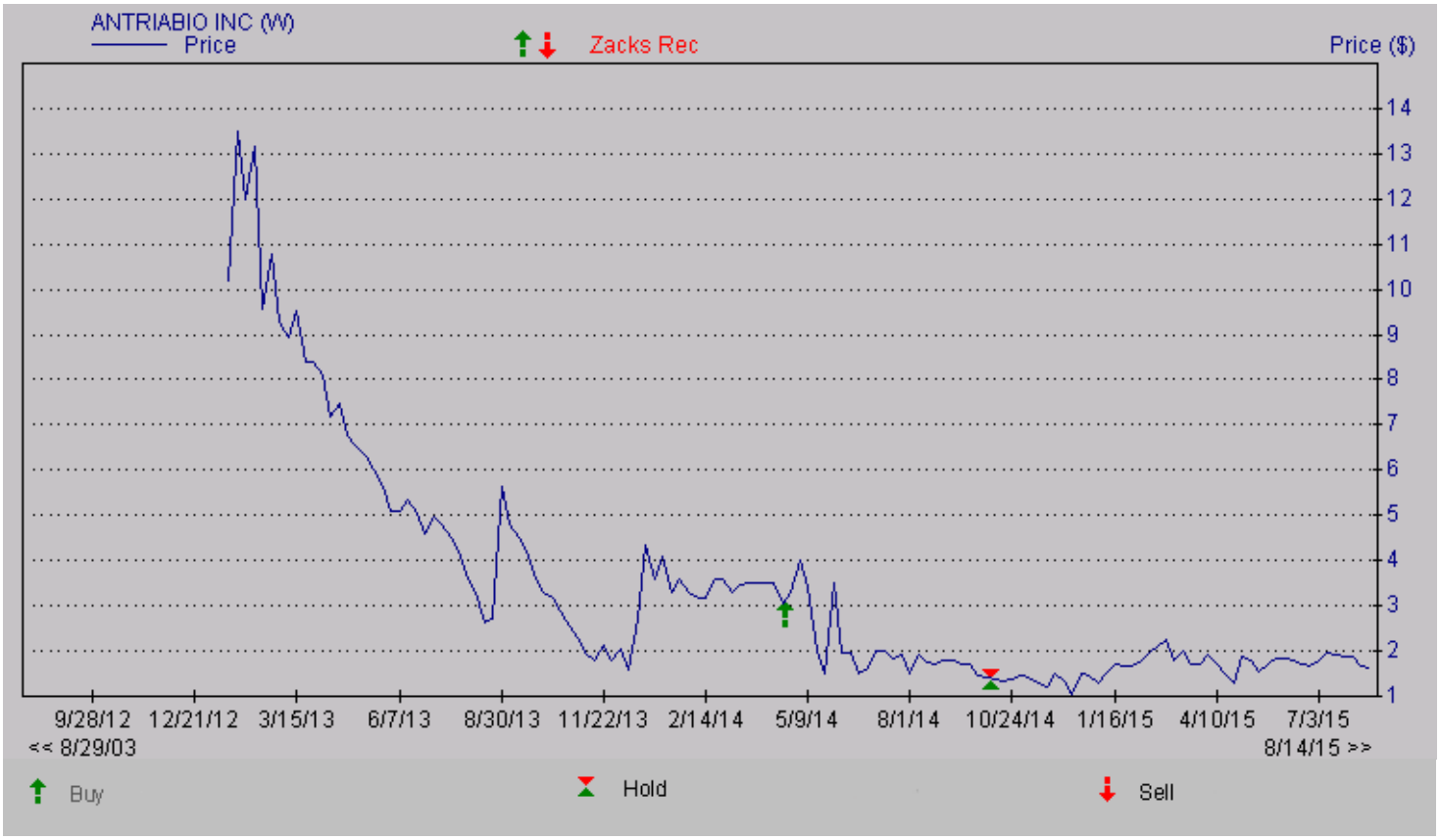
We have built a financial model forecasting the risk-adjusted potential cash flow from selling AB101 on a global basis. Our assumptions include filing the U.S. NDA in 2019 and launching the product in 2020. We model peak sales of $3.5 billion in 2027 with 70% net operating margin at peak. We assuming exclusivity at 100% until 2024 and then risk-adjust the cash flow from 2025 to 2035 down by 50% until the new patents around the manufacturing process have been granted. We assume 10% probability of success at this stage. Accordingly, we think the shares are still worth approximately $2.25 right now. We believe that positive Phase 1/2 data in 2016 would cause us to raise our probability of success from 10% to 30%, bringing the valuation to roughly $8 per share.

## AntriaBio, Inc. - Income Statement

| AntriaBio, Inc. | FY '14 A | Sept '14 A | Dec '14 A | Mar '15 A | Jun '15 E | FY '15 E | FY '16 E |
|---|---|---|---|---|---|---|---|
| AB101 Sales / Royalties | $0 | $0 | $0 | $0 | $0 | $0 | $0 |
| *YOY Growth* | - | - | - | - | - | - | - |
| Licensing / Collaborative | $0 | $0 | $0 | $0 | $0 | $0 | $0 |
| *YOY Growth* | - | - | - | - | - | - | - |
| **Total Revenues** | **$0** | **$0** | **$0** | **$0** | **$0** | **$0** | **$0** |
| *YOY Growth* | - | - | - | - | - | - | - |
| CoGS | $0 | $0 | $0 | $0 | $0 | $0 | $0.0 |
| *Product Gross Margin* | - | - | - | - | - | - | - |
| R&D | $0.03 | $0.1 | $1.6 | $1.3 | $3.0 | $6.0 | $15.0 |
| SG&A + Other | $5.1 | $2.1 | $1.5 | $1.0 | $1.8 | $6.4 | $10.0 |
| Operating Income | **($5.2)** | **($2.2)** | **($3.1)** | **($2.3)** | **($4.8)** | **($12.4)** | **($25.0)** |
| *Operating Margin* | - | - | - | - | - | - | - |
| Interest & Other Income | ($4.6) | $0.0 | $0.1 | ($0.9) | $0.2 | ($0.6) | $0.5 |
| Pre-Tax Income | ($9.7) | ($2.2) | ($2.9) | ($3.2) | ($4.6) | ($12.9) | ($24.5) |
| Taxes & Other | $0 | $0 | $0 | $0 | $0 | $0 | $0 |
| *Tax Rate* | *0%* | *0%* | *0%* | *0%* | *0%* | *0%* | *0%* |
| Net Income | ($9.7) | ($2.2) | ($2.9) | ($3.2) | ($4.6) | ($12.9) | ($24.5) |
| *Net Margin* | - | - | - | - | - | - | - |
| **Reported EPS** | **($1.04)** | **($0.12)** | **($0.16)** | **($0.14)** | **($0.19)** | **($0.62)** | **($0.61)** |
| *YOY Growth* | - | - | - | - | - | - | - |
| Basic Shares Outstanding | 9.4 | 18.1 | 18.9 | 22.5 | 24.3 | 21.0 | 40.0 |

*Source: Company Filing // Zacks Investment Research, Inc. Estimates*

## HISTORICAL ZACKS RECOMMENDATIONS



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Buy/Outperform: The analyst expects that the subject company will outperform the broader U.S. equity market over the next one to two quarters.
Hold/Neutral: The analyst expects that the company will perform in line with the broader U.S. equity market over the next one to two quarters.
Sell/Underperform: The analyst expects the company will underperform the broader U.S. Equity market over the next one to two quarters.

The current distribution is as follows: Buy/Outperform- 28.1%, Hold/Neutral- 54.0%, Sell/Underperform – 14.9%. Data is as of midnight on the business day immediately prior to this publication.