Zacks Small-Cap Research

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AntriaBio, Inc. (ANTB-OTC)

ANTB: Bullish On Long-Acting Insulin, But AntriaBio Has Work To Do…

Current Recommendation	**Neutral**
Prior Recommendation	N/A
Date of Last Change	10/07/2014
Current Price (11/12/14)	$1.21
Target Price	**$1.15**

Update

We believe AB101 has peak sales in the area of $2.5 billion by 2024. Only investors today certainly do not need to wait around to 2024 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 / 2a data has been generated. Based on historical "big pharma / small-biotech" partnerships, we believe AntriaBio can capture 10% of the peak sales of AB101 prior to approval in 2020. This equates to $250 million in milestone payments, of which we assume $100 million will come in the form of an upfront payment, $50 million for the completion of Phase 3 studies, and $100 million for approval. We also believe AntriaBio can capture 20% royalties on sales plus another $500 million in potential back-end milestones. We assume 20% probability of success and 30% discount rate on our 10-year DCF model. This equates to $60 million present value, or $1.15 per share.

SUMMARY DATA

52-Week High	**$4.44**
52-Week Low	**$1.21**
One-Year Return (%)	**-58.80**
Beta	**-2.75**
Average Daily Volume (sh)	**6,806**
Shares Outstanding (mil)	**18**
Market Capitalization ($mil)	**$24**
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 E	0 E	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	-$0.10 E	-$0.13 E	-$0.14 E	-$0.50 E
2016					-$0.65 E
2017					-$0.75 E

WHAT'S NEW

AntriaBio's AB101 – The First Once Weekly Basal Insulin

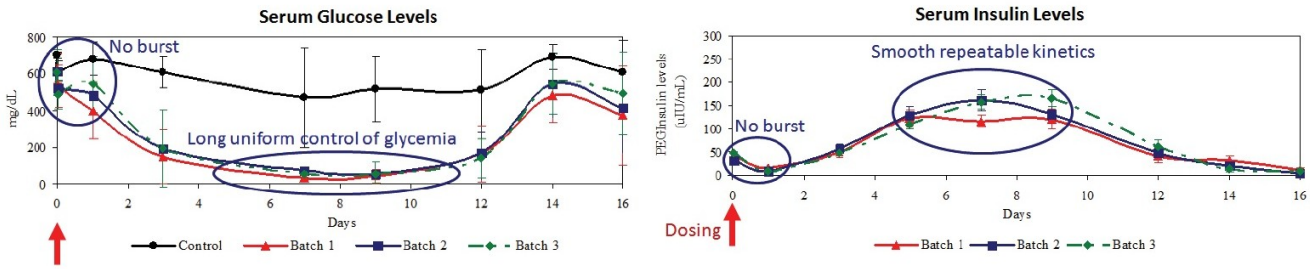
AntriaBio is developing AB101, a product that aims to be the first once weekly basal insulin. AB101 is a formulation of human recombinant insulin (non-analog) for subcutaneous injection that is designed to release insulin slowly and uniformly over a period of approximately one week without an adverse initial burst. AB101 is a proprietary formulation developed by the company to preserve the integrity and biological activity of insulin through the manufacturing process. And, 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 poly-lactic-co-glycolic acid (PLGA). 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.

We think AB101 offers several significant advantages over Sanofi's Lantus (insulin glargine).

- ✓ **Improved compliance**: A systemic review of dosing regimens conducted by Claxton MS PhD et al., 2001, published in the Journal of Clinical Therapeutics (Vol.23,No.8:1296-1310) found that dosing compliance improved dramatically with less frequent dosing. Data show 79% compliance to once daily dosing (QD), vs. 69% compliance to twice daily (BID) and only 65% compliance to three-times daily (TID). For once weekly dosing, a study conducted by Emkey et al, 2006, and published in The American Journal of Medicine (Vol.119:18s-24s) found that 59% of patients remained fully compliant to once weekly dosing after 12 weeks vs. only 38% full compliance to once daily dosing after 12 weeks.

- ✓ **Improved kinetics**: AntriaBio has generated preclinical data showing a pharmacokinetic and time-action profile for glucose (pharmacodynamic) which compares favorably to the well-established profiles and duration of action for existing long-acting insulins such as Lantus. The data show 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. There was no reduction in the integrity of biologic activity of the insulin in AB101.

- ✓ **No initial burst**: AB101 reduces the risk of the initial burst of basal insulin, reducing risk of hypoglycemia. The company has also been able to demonstrate minimal peak-to-trough variation after the second injection and a repeatable patter from one injection to the next.



- ✓ **Better safety**: The company believes, and we concur, that once weekly injection of AB101 will result in reduced incidence of injection site reaction.

…Where Others Have Failed – AB101 May Succeed…

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 polylactic , polyglycolic (PLGA), or polyglutamate (pGlu) microspheres.

- **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.

  PEG is readily available in various sizes (molecular weight). Molecular weights of PEG used in biomedical applications usually range from a few hundred to 20,000 Da. PEGylated drugs are generally recognized as safe for human use by the U.S. FDA. Generally, the larger the molecular weight PEG attached to the target molecule, the longer the body takes to clear. PEG also protects from metabolism and degradation of exogenously delivered therapeutics. However, in order to create a PEG-insulin with the necessary stability and circulation to allow for once weekly dosing, large-molecule-weight PEG (20kDa or greater) must be conjugated to insulin. Studies (Kawai et al, 2002) show that ultra long-acting PEGylated compounds may have unpredictable clearance times and may lead to the accumulation in the liver, leading to inclusion bodies with unknown toxicologic consequences. Additionally, degradation or alteration in the large-molecule-weight PEG chain may lead to unexpected or unpredictable clearance times *in vivo* (Veronese et al, 2001).

  Other research suggests that large-molecule PEG conjugated to insulin may interfere with its interactions with the insulin receptor, reducing activity to stimulate transport of glucose into the cell, given the size of the molecule or fragile nature of the engineered construct. This creates issues with bioactivity and potentially manufacturing yield. This would seem to suggest that Lilly's LY2605541 may run into problems.

  Therefore, it seems a safer approach to conjugate low-molecule-weight (<5kDa) PEG to insulin. Data from Hinds et al, 2002, and published in Advanced Drug Delivery Reviews (Vol.54:505-530) imply that site-specific attachment of low-molecular-weight PEG (mPEG) to insulin does not substantially alter insulin's secondary / tertiary structure, self-association behavior, or potency *in vivo*. However, mPEG attachment did significantly enhance insulin's resistance to aggregation, as well as almost completely eliminated the immunogenicity, allergenicity, and antigenicity. Therefore, mPEG seems to have the same desirable effects as large-molecule PEG, but without the risk of inclusion bodies or issues with alteration in protein folding and efficacy / potency to stimulate glucose transport into the cells.

- **Encapsulation**: Encapsulating insulin in polylactic , polyglycolic (PLGA), or polyglutamate (pGlu) microspheres is a strategy designed to extend delivery of dose by allowing slow release of the insulin as the encapsulating microspheres are slowly broken down by contact with water over a controlled period of time (usually 1 to 14 days). The benefit to encapsulation is that the target therapeutic agent, in this case insulin, is unmodified and remains biologically active similar to the native molecule after release.

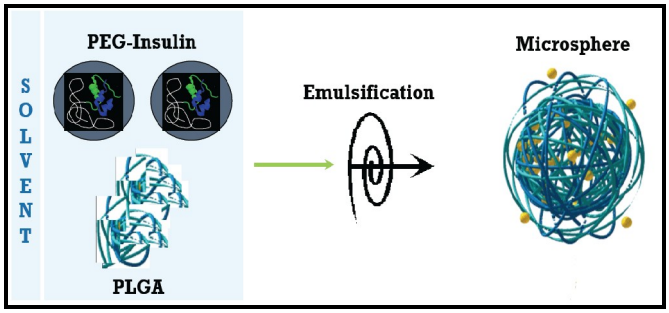
  While encapsulation in microspheres sounds like a good idea with respect to maintaining biological activity, issues with microspheres include the unpredictable burst effect of the depot formation, site-specific adverse events / poor tolerance, and variations of dose administration (subcutaneous vs. intramuscular). Research done by Yeo et al, published in the Achieves of Pharmaceutical Research in January 2004 (Vol.27,No.1:1-12), notes that initial burst of protein with encapsulation is a "major challenge in protein-encapsulated microparticle systems." The authors find that 20% initial burst or greater is common with PLGA encapsulation.

From available literature, **WE CONCLUDE** that PEGylation does a very good job of extending circulation and conferring stability on the molecule. However, large-molecular-weight PEGylation, the kind that would be necessary to obtain extended dosing beyond a day or two in the absence of a depot formulation, impacts biologic activity and could lead to liver-specific toxicity. Low-molecular-weight PEGylation does not seem to alter biologic activity or create inclusion bodies, but not does deliver the sustained circulation to obtain once weekly dosing (Hinds et al, 2002). Encapsulation does not alter biologic activity, but does not seem to overcome the risk of burst effect or site-specific adverse events when administered daily (Yeo et al, 2004).

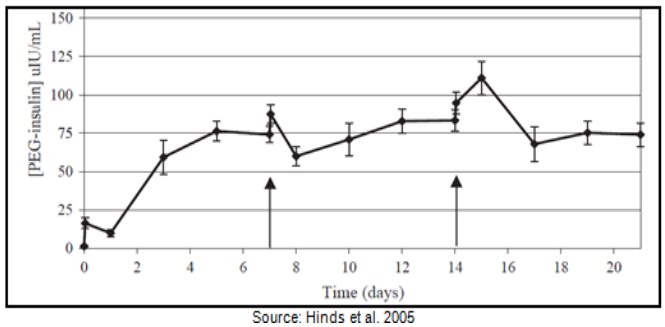
Therefore, AntriaBio's strategy to create AB101 was simple – encapsulate low-molecular-weight PEG-modified insulin. In theory, AB101 should retain the biological activity of insulin, with extended circulation and stability, without burst effect. The company's preclinical data suggests that PEGylated insulin inside PLGA microspheres offers exceptionally low burst release *in vitro* and *in vivo*, a desirable near zero order kinetic profile, and substantially complete release of encapsulated protein (93% over 16 days). Biological activity was confirmed to be non-inferior to daily basal insulin when evaluated on a number of parameters = C_{MIN}, T_{MIN}, and AUC.

PEG-insulin microspheres administered subcutaneously as a single injection produced < 1% release of insulin in the first day but then lowered the serum glucose levels of diabetic rats to values < 200 mg/dL for approximately 9 days. When doses were given at 7-day intervals, steady state drug levels were achieved after only 2 doses. The chart below shows the mean (±SE) serum insulin levels in diabetic rats (n=10) following repeat once weekly subcutaneous administration of PLGA/PEG-insulin microspheres. This preclinical data was published in the Journal of Controlled Release (Hinds et al, 2005).

AB101 Process



Serum Insulin Levels



Source: Hinds et al. 2005

…Clinical Development Plans…

The near-term development plans with AB101 consists of:

1. Complete remaining pre-clinical studies to support U.S. IND filing:

With respect to the specific data that needs to be completed prior to the U.S. pre-IND meeting with the U.S. FDA, AntriaBio intends to conduct a number of preclinical studies to generate the necessary pharmacokinetic and pharmacodynamic data to support the application. According to management, the company has completed most of the critical analytical methods for AB101, including determining the strength and release profile of the drug as well as other physical and chemical attributes such as particle size and residual solvents. The previous developer of AB101, PR Pharmaceuticals, conducted small animal studies (rat models) to generate pre-IND data. AntriaBio must generate chemistry and manufacturing data to support GMP scale up work. AntriaBio believes that AB101 will qualify as a new molecular entity (NME), and thus requiring a standard list of preclinical IND-enabling work. We expect some of these preclinical studies will include:

- GLP toxicity studies (estimated to initiated in the fourth quarter of calendar 2014)
- Acute and sub-acute toxicity studies in at least two species, likely rodents and dogs (first half of 2015)
- Safety pharmacology studies (first half of 2015)
- Mutagenicity / genotoxicity studies (first half of 2015)

However, before AntriaBio can progress to filing an IND, the company must make manufacturing facility improvements at their plant in Louisville, CO. Facility improvements including fixing or updating existing equipment along with buying new equipment. Management estimates the cost of building the cGMP suite and making the necessary improvements will be roughly $3.5 million. This will need to take place over the next several months in order to move AB101 into human studies. Unfortunately, with a cash balance of only $4.3 million as of September 30, 2014, the company does not have enough funds to make the facility construction and improvements necessary. Management estimates they will require $10 million to bring AB101 into human clinical development.

2. File U.S. IND

If management can raise the necessary funds to complete the construction and improvements necessary at the manufacturing facility, the next step after all IND-enabling data has been generated is to filing the U.S. IND application. AntriaBio believes that AB101, a PEGylated, encapsulated human recombinant insulin, 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, and encapsulation, 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.

3. Initiate Phase 1 / 2a clinical studies in the U.S.

The objectives of the Phase 1 program will be to assess the single and repeat (once weekly) ascending dose safety, pharmacokinetics (PK), and pharmacodynamics (PD) in the target population with type 1 and type 2 diabetes, including confirmation of the time action profile for glucose lowering (Phase 2a data).

4. Move into Phase 2b / Phase 3 clinical studies in the U.S.

Following successful completion of the Phase 1 / 2a program, Phase 2b trials in both type 1 and type 2 diabetes will be conducted to obtain proof-of-concept for the intended once weekly dosing regimen. These trials will use accepted biomarkers for glucose efficacy (i.e. HbA1c), compared to a standard of care basal insulin such as Sanofi's Lantus (glargine). If 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 1 / 2a 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 Phase 1 / 2a data can be generated by the middle of 2016 if AntriaBio can obtain the necessary funding.

Cash Requirement Looms Large

As of September 30, 2014, the company held $4.2 million in cash and investments. AntriaBio burned $1.6 million in cash from operations and investments for the three month period ending September 30, 2014. The company financed operations over the past several months primarily through the offering of common stock and convertible notes. In order to complete the necessary preclinical and clinical work to generate data sufficient to secure a global development and commercialization partnership on AB101, AntriaBio will require significant cash. Above we noted they need roughly $10 million in new funds. We believe this will take place before the end of the calendar year 2014. AntriaBio's current basic market capitalization is $22 million. We believe raising an additional $10 million will be a daunting task (40% dilutive) and is our primary reason for the current 'Neutral' rating.

Taking A Stab At The Valuation

We believe AB101 has peak sales in the area of $2.5 billion by 2024. Only investors today certainly do not need to wait around to 2024 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 / 2a data has been generated. Catalysts prior to late 2016 include:

Catalyst	Timing
Complete IND Tox Work	**Q1-2015**
Large Animal Study Data	**Q2-2015**
File IND	**Q3-2015**
Begin Phase 1 Study	**Q3-2015**
Phase 1 Data	**Q4-2015**
Begin Phase 2a Studies	**Q1-2016**
Phase 2a Data	**Q3-2016**
Sign Partnership Agreement	**Late 2016**

Based on historical "big pharma / small-biotech" partnerships, we believe AntriaBio can capture 10% of the peak sales of AB101 prior to approval in 2020. This equates to $250 million in milestone payments, of which we assume $100 million will come in the form of an upfront payment, $50 million for the completion of Phase 3 studies, and $100 million for approval. We also believe AntriaBio can capture 20% royalties on sales plus another $500 million in potential back-end milestones. We assume 20% probability of success and 30% discount rate on our 10-year DCF model. We have also added in 10 million shares + 10 million warrants at $1.00 per share to account for the required $10 million in necessary funds to move AB101 through Phase 2a studies. This equates to $60 million present value, or $1.15 per share.

AntriaBio	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	TERM
Estimate Market For LAI	$10,000	$11,000	$5,500	$6,875	$8,250	$9,488	$10,626	$11,689	$12,857	$14,143	$15,558	
Stage	pre-IND	IND / P1	P2a / Partner	P2b	P3	NDA	Approved					
Estimated AB101 Market Share	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*2%*	*5%*	*10%*	*15%*	*16%*	
Estimated AB101 Sales	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$213**	**$584**	**$1,286**	**$2,121**	**$2,489**	
Upfront			$100									
Regulatory					$50		$100					
Backend									$100	$150		
Royalties (~20%)							$43	$117	$257	$424	$498	
Total Pennsaid Revenues	**$0**	**$0**	**$100**	**$0**	**$50**	**$0**	**$143**	**$117**	**$357**	**$574**	**$498**	**$747**

Discount Rate	**30%**	Current Cash	$4				
Probability	**20%**	Required Cash To Partner	($20)		**Fully Diluted**	38.2	
ANTB NPV	**$60**	Net Cash	($16)		**TARGET**	**$1.15**	NOW

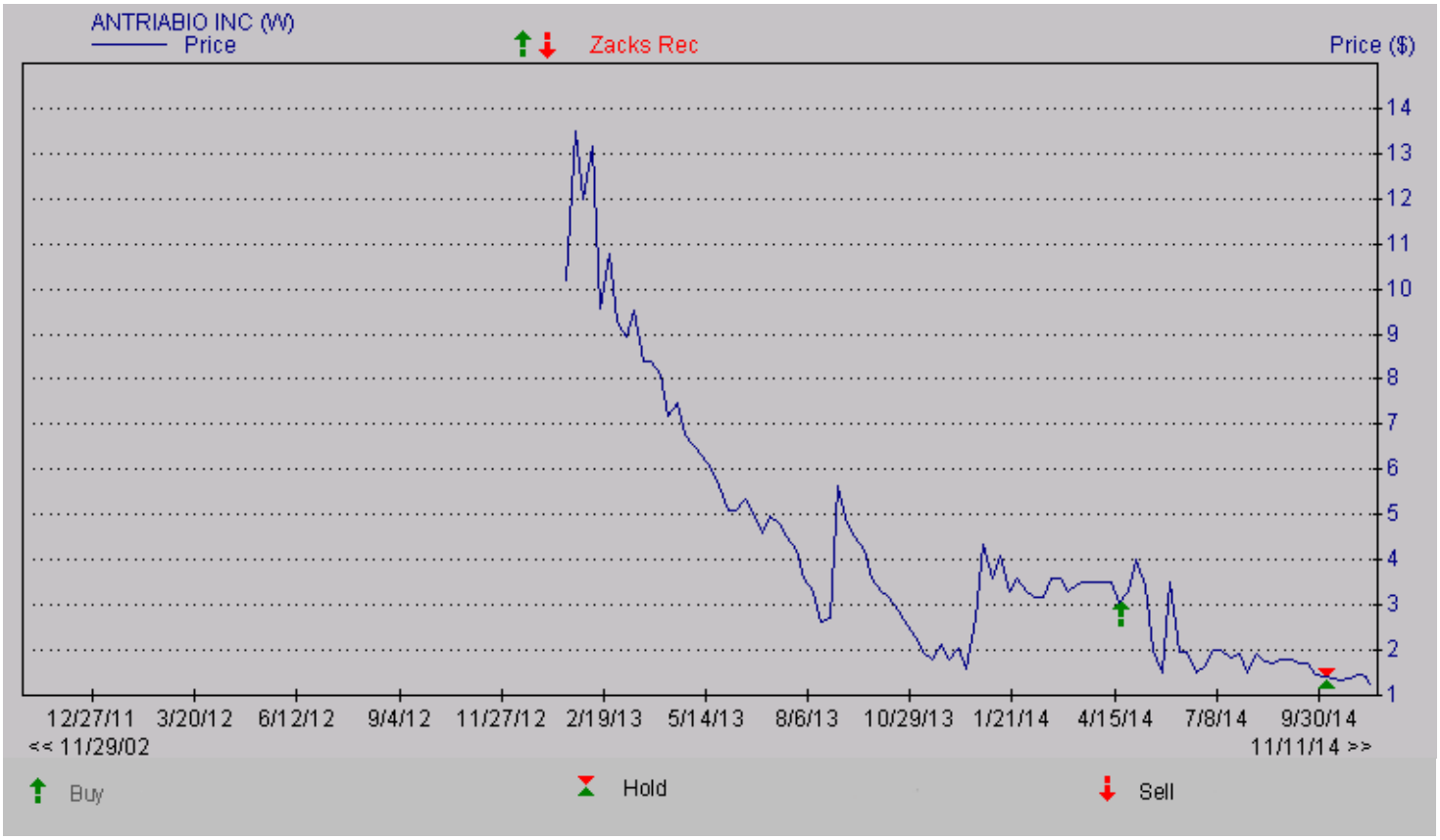
Source: Jason Napodano, CFA

AntriaBio, Inc.
Income Statement

AntriaBio, Inc.	FY '14 A	Sept '14 A	Dec '14 E	Mar '15 E	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	$0.034	$0.123	$0.500	$1.000	$1.500	$3.123	$15.000
% R&D	-	-	-	-	-	-	-
SG&A + Other	$5.142	$2.113	$2.000	$2.500	$2.500	$9.113	$10.000
% SG&A	-	-	-	-	-	-	-
Operating Income	($5.176)	($2.235)	($2.500)	($3.500)	($4.000)	($12.235)	($25.000)
Operating Margin	-	-	-	-	-	-	-
Interest & Other Income	($4.554)	$0.020	($0.200)	($0.200)	($0.200)	($0.580)	($1.000)
Pre-Tax Income	($9.730)	($2.215)	($2.700)	($3.700)	($4.200)	($12.815)	($26.000)
Taxes & Other	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	($9.730)	($2.215)	($2.700)	($3.700)	($4.200)	($12.815)	($26.000)
Net Margin	-	-	-	-	-	-	-
Reported EPS	**($1.04)**	**($0.12)**	**($0.10)**	**($0.13)**	**($0.14)**	**($0.50)**	**($0.65)**
YOY Growth	-	-	-	-	-	-	-
Basic Shares Outstanding	9.4	18.1	26.0	28.0	30.0	25.5	40.0

Source: Zacks Investment Research, Inc. *Jason Napodano, CFA*

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- 16.8%, Hold/Neutral- 75.5%, Sell/Underperform – 6.7%. Data is as of midnight on the business day immediately prior to this publication.