

Buena Vista Investment Management, LLC

Creative Investment Solutions

Update on Isis Pharmaceuticals November 2012

We wanted to provide you an update on your investment in Isis Pharmaceuticals as there has been a great deal of new information on the company over the last few weeks.

RECENT EVENTS:

1. In August and September, the company completed redemption of its existing convertible debentures and issued new debentures on favorable terms for the company.
2. In October, Regulus Therapeutics, a company co-founded by Isis went public. Isis stake in the company at the IPO price was \$28 million. After the IPO Isis is eligible to receive fees and or royalty payments on microRNA products that Regulus or its partners develop.
3. In October, the FDA Advisory Committee recommended that the FDA approve Kynamro for use as an orphan drug for Homozygous Familial Hypercholesterolemia.
4. In November, Isis reported that it received a \$1.25 million payment for EXC 001 from Pfizer after Pfizer decided to move the compound into new Phase 2 trials. Isis is eligible to receive an additional \$8.35 million in milestone payments as EXC 001 moves forward in the commercialization process.

KYNAMRO:

Of the four items listed above the most significant item was that the FDA Advisory Committee recommendation on Kynamro. If Kynamro is approved for use in the EU and USA, this will be the most important event since the company's founding in 1989. It will also be an important step towards validating "Antisense Technology" as a viable drug discovery platform. Kynamro is the first drug to use the 2nd generation antisense chemistry developed by Isis.

It is anticipated that the company will receive an indication of approval/disapproval on Kynamro from the EU before year end and from the FDA during the first quarter 2012.

INVESTMENT IN ISIS:

Notwithstanding all of the recent news on Isis (good from my perspective), we have seen the stock hit an intraday high of \$15.61 at the end of September only to fall to its present level of approximately \$8.50. It would be an understatement to describe the stock's recent price action as disappointing but as an investor our responsibility is to determine if the decline in price was warranted or market overreaction.

After completing our due diligence, we have determined that continued retention of Isis and the purchase of additional shares of the company, where appropriate is the best approach for our client investments. Additional detail on the next page...

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Update on Isis Pharmaceuticals (continued)

INVESTMENT IN ISIS (continued):

Our due diligence included personal conversations with Isis employees; Amy Blackley PHD (Investor Relations) and Kristina Lemonidis PHD (on the original team that discovered the Kynamro compound and currently working on the physician education team for the use of this drug, previously Investor Relations); Discussions with Dr. T. Bash MD relating to medical issues surrounding clinic trials and FDA Advisory Committee documents; review of FDA transcripts and Isis conference call transcripts.

IMPORTANT DATA ON ISIS PHARMACUTICALS: As detailed below there are a number of very interesting data points to be considered when reviewing an investment in Isis. **First**, the company has 25 active compounds in clinical trials or approved for use. To the best of our knowledge, there is no other biotechnology company, the same size as Isis, that has this many compounds under consideration. **Second**, to the best of our knowledge there is no other biotechnology company with a business model that compares to Isis (\$517 million in revenue over the last 5 years from collaborative partnerships and has no FDA approved products). **Third**, to the best of our knowledge there is no other biotechnology company that has 23 compounds in clinical trials and has been able to maintain a stable current asset position on their balance sheet, without an approved product.

Compounds in Clinical Trials (all information taken from company website)

	<u>2009</u>	<u>2012</u>
Pre-Clinical	7	5
Phase I	6	6
Phase II	7	11
Phase III	1	2
Approved	1	2
Total	22	25

Company Revenues (all information taken from company 10K or 10Q reports)

2008	\$107MM
2009	\$121MM
2010	\$108MM
2011	\$99MM
9-30-12	\$82MM

Balance Sheet Data (all information taken from company 10K or 10Q reports)

	Total		Short-Term
	<u>Current Assets</u>	<u>Cash</u>	<u>Investments</u>
2008	\$518	\$217	\$273
2009	\$596	\$105	\$469
2010	\$483	\$70	\$402
2011	\$360	\$65	\$278
9-30-12	\$361	\$84	\$259

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Update on Isis Pharmaceuticals (continued)

INVESTMENT CONCLUSIONS:

Our original investment in Isis Pharmaceuticals occurred in 2003, approximately 9 years ago. Over that time we have seen the stock sink on disappointing results for a 1st generation cancer drug and soar on the initial news concerning a compound called Mipomersen (today called Kynamro). Our investment in this bio-tech company has been a long and winding road.

Recent events have caused us once again to examine the investment premise behind Isis Pharmaceuticals. Our thoughts are as follows;

MANAGEMENT – The existing management team has been in place for the entire tenure of our investment. Dr. Stanley Cooke CEO and Lynne Parshall CFO have guided this company to a robust potential pipeline of products and a stable balance sheet. We have tremendous confidence that this team can take Isis to the next level.

BUSINESS STRATEGY – The game plan developed by Dr. Crooke is to make Isis a drug discovery company and not a drug company. This is a very important distinction that has to be drawn when discussing our investment in Isis. The genetic patents (aka the Crooke patent estate) accumulated by the company over the last 20 years is another differentiating factor when looking at Isis as an investment. The foresight to accumulate genetic information and licensing its technology/data is the primary factor for the company's stable balance sheet. The ability to generate over \$500 million in revenue without any products formally being sold to the public is a testament to the company's overall business strategy.

THE SCIENCE – The Antisense Technology drug discovery platform is the key to this investment. Isis is trying to build this unique technology into a platform for discovering new medicines. This is not an easy task and honestly, one that has taken longer than anticipated. That is what makes Kynamro so important to the company, as I believe, approval will validate the platform.

BOTTOM LINE – We are within six months of knowing how good of an investment Isis Pharmaceuticals is going to be or not be for us. As an investor that believes in the management team, the business strategy and the science, we remain a patient investor, building a position to create wealth for our clients in the future.

Respectfully Submitted,
John L. Moffat, Partner
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