

# *Buena Vista Investment Management, LLC*

*Creative Investment Solutions*

## Isis Pharmaceuticals

On June 2, 2010 I attended the annual meeting for Isis Pharmaceuticals (Ticker – ISIS Web Site – [isispharma.com](http://isispharma.com)). After the annual meeting I was able to spend some “one on one” time with the company’s CEO, CFO and scientists in charge of drug discovery. The following is a recap from some of those discussions and various presentations made by Isis over the past six months. I have also included some slides prepared by the company which I hope will help you better understand the investment dynamics of Isis Pharmaceuticals.

Buena Vista Investment Management began investing in Isis in 2004 based on our belief that their genetic research and unique approach to discovering new drugs would eventually lead to a much higher stock price. Since that first investment six years ago, we have seen many ups and downs, but from our perspective Isis Pharmaceuticals, has never been in better financial shape and we remain confident in the investment premise. We continue to add to existing investment positions and to initiate new positions for clients.

### **Background:**

Isis Pharmaceuticals was founded in 1989 by its current chairman and CEO Dr. Stanley Crooke. The company became a publicly traded company in 2001.

Currently, there are two validated approaches to drug discovery; Small Molecule and Protein Therapy. Isis has been working for the last 20 years to make Antisense Technology the third validated drug discovery platform. Antisense Technology is a drug discovery platform based on genetics. The end result of all three platforms is the same and can be simply described as; find a molecule that will destroy a protein which is causing a disease in the human body.

In the Isis Pharmaceuticals 2009 annual report the company made a bold prediction; ...“our broad Antisense Technology platform is positioned to change the productivity of the pharmaceutical industry.” Over the next 5 years, we as investors will know definitively if this was a bold forward looking statement or an idle boast.

### **Management:**

It is important to emphasize that investing in a biotechnology company is a long-term investment and given the nature of the business it would also be considered a risky investment. As such, management of the company is an extremely important component when selecting a biotech investment. Over the years I've had access to Chairman and CEO, Dr. Stanley Crooke on a number of occasions and strongly believe that his management is the cornerstone of our investment. His vision for genetic research has allowed the company to gather over 1600 worldwide patents relating to genetic drug discovery over last 20 years. In addition, his business strategy of positioning Isis to be a drug discovery company rather than a pharmaceuticals company gives us as investors, in my opinion the best chance of financial success.

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### **Financials:**

For a biotechnology company the need for capital is always a major concern. From our prospective, Isis is in its best financial shape since its original public offering. The company ended 2009 with \$596MM in current assets and only \$111MM in current liabilities. The company is projected to end 2010 with over \$400 million in cash and Mipomersen; the company's new flagship drug should be presented to the FDA for approval in 2011. According to Dr. Crooke, the company should generate positive net income in 2011... if Mipomersen achieves FDA approval.

Since our original investment, the company has had to access the capital markets only once, when they completed a pipe financing in 2005. This capital raise in conjunction with the sale of Ibis Biosciences in 2009 and a host of strategic partnerships have Isis positioned for financial success.

### **Corporate Strategy:**

The strategy for Isis is to be a drug discovery company and not a drug company. In other words Isis will use its resources to bring new drugs through the "proof of concept" process. Proof of concept would be defined as Preclinical (animal trials) and Phase 1 clinical trials. Isis will then partner with a larger drug company and use their financial strength and expertise to bring the potential new drug through Phase 2 and Phase 3 trials and final regulatory approval, here and internationally.

These unique partnership agreements have allowed Isis to currently have 22 compounds into clinical trials, an unheard of number for a company of this size (See Page 7). Without this partnership approach, Isis would not have the resources to have even a third of these compounds in trials. From our perspective as investors, this corporate strategy gives us a better chance at success, as drug discovery is a risky and uncertain business. The more opportunities we have to succeed the greater likelihood of our success. Additionally, the partnerships currently in place have generated over \$650 million of cash to Isis over the past three years. (See Pages 8-9)

Part two of the corporate strategy is to focus the company's drug discovery processes on current unmet medical needs; defined as rare or orphan diseases. The company believes that this approach serves two purposes; first because they are dealing with orphan diseases for which the patient population may not have any alternatives for treatment, so human trials and regulatory approval should occur in a shorter time. Second, if patients with severe diseases are helped by Isis compounds then this will in turn help validate Antisense Technology.

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### **Corporate Strategy:** (continued)

For example, the company is currently completing phase 3 trials, in conjunction with Genzyme, for their new drug Mipomersen, which is a cholesterol lowering drug. Rather than competing directly with a whole host of lipid lowering drugs, Isis is focusing their clinical trials on individuals that have extremely high cholesterol (hypercholesterolemia). These patients have a significant risk of cardiovascular events due to the fact that their disease cannot be controlled with current lipid lowering therapy, such as Lipitor. So far, in two Phase 3 trials this patient population has seen their LDL's lowered by 25% in conjunction with traditional lipid lowering treatment. This is an extremely large percentage decline in "bad" cholesterol. So by focusing on this unusual patient population, Isis is working on an unmet medical need while still validating their technology.

Antisense Technology is a totally new and unique drug discovery platform. For us as investors this can create a huge monetary opportunity if the technology is validated. The technology is described on the Isis website in the following manner;

"The explosion in genomic information led to the discovery of many new disease-causing proteins and created new opportunities accessible only to antisense technology. We have led the industry in the development of RNA-based technologies and successfully developed a drug discovery platform based on our antisense technology. We discover and develop drugs that bind to RNA instead of proteins, which have been the focus of the pharmaceutical industry for more than 100 years."

The beauty of this genetic based drug discovery platform is that the cost to bring a drug to market is substantially less than traditional small molecule drugs (See Pages 5). Additionally, the probability of reaching clinical trials is substantially higher than small molecule drugs which in turn gives Isis pharmaceuticals a unique financial edge who over a traditional drug discovery company.

### **The Future:**

Some important points relating to the investment in Isis Pharmaceuticals

1. *Antisense Technology is about to get an upgrade.* The current technology is called 1st Generation. The company is close to beginning use of 2nd Generation compounds which according to the company are 10 times more potent than the original compounds. The company also believes that oral administration will be achieved with Generation 2.5.

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### **The Future:** (continued)

2. *The Crooke Patent Estate.* The company's patent estate is named after its founder and includes over 1,600 patents relating to genetic information. This patent estate has been built over the last 20 years as Isis has acquired or filed for patents on all kinds of genetic information. The company feels that this is an important asset that Wall Street has overlooked when valuing the company.
3. *Manufacturing Process for Future Drugs* – The beauty of the Antisense drug discovery platform is that it allows for drugs to be brought to market for substantially less cost than other drug discovery platforms. But it doesn't end there; the actual manufacturing process for these drugs will also cost less. This genetic platform begins with the same formulation, for all kinds of varied drugs, which means it will cost less to manufacture these drugs when compared to traditional small molecule drug.

In closing, It is difficult to try and explain a complex process like Antisense Technology without getting into too much detail. It is our hope that this short recap and the included slides will help you understand why we, as investors, are excited about the future for this investment.

Please feel free to contact us with any questions relating to Isis Pharmaceuticals.

John Moffat, Partner  
Buena Vista Investment Management, LLC

# Efficiency of Antisense Platform

	Antisense Drugs			Small Molecule Drugs		
<i>Idea to Phase 1</i>	<u>Cost</u> \$5-10M	<u>Time</u> 2 - 5 yrs	<u>FTE/yr</u> 3 - 5	<u>Cost</u> \$40-100M	<u>Time</u> 7 - 10 yrs	<u>FTE/yr</u> 20 - 40
<i>Preclinical Development</i>	~90% probability of reaching clinical trials			~10% probability of reaching clinical trials		
<i>CMC Investments</i>	Investments amortize over entire pipeline			Unique investments required for each drug		
<i>TOX/PK</i>	Similar for all drugs No drug interactions			Unique for each drug		
<i>Breadth of Opportunities</i>	All genes Major tissues			Only “druggable” targets		

# Advantages

## Antisense Platform Technology

Only Direct Route  
from Genes to Drugs

*Uniquely specific &  
broadly applicable*

Efficient Discovery &  
Early Development

*Dramatically reduced cost &  
increased success in R&D*

Investment Amortized  
Across the Entire Pipeline

*Chemistry, manufacturing,  
formulation, analytical methods*

Generate an  
Evergreen Pipeline

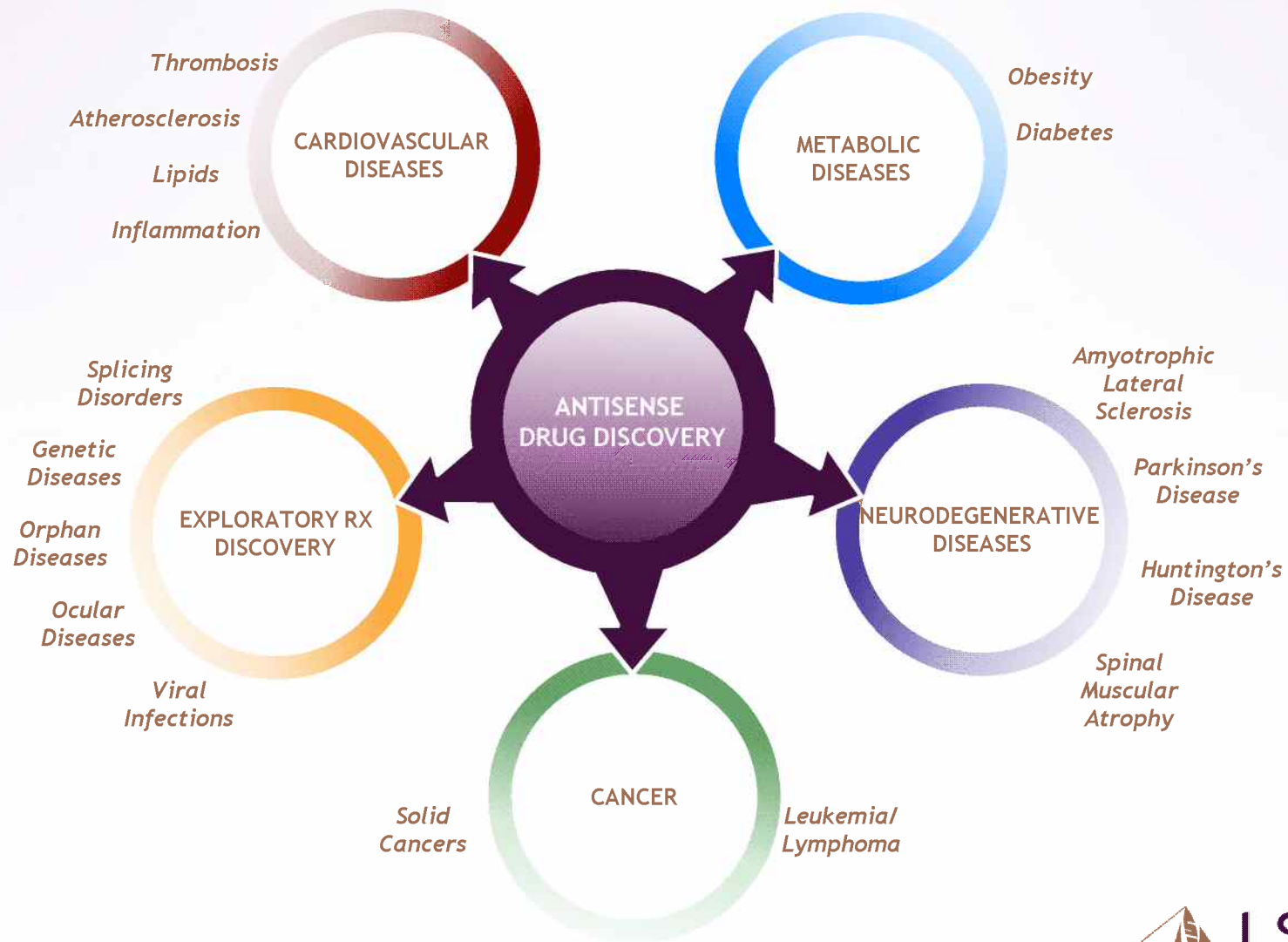
*Robust, diversified pipeline  
adding 3-5 new drugs per year*

# Pipeline

■ partnered

PROJECT	INDICATION	TARGET	PRECLINICAL	PHASE I	PHASE II	PHASE III	APPROVED
CARDIOVASCULAR							
Mipomersen	High Cholesterol	apoB					genzyme
ISIS-CRP <sub>Rx</sub>	CAD/Inflammation/Renal	CRP					
BMS-PCSK9 <sub>Rx</sub>	CAD	PCSK9					Bristol-Myers Squibb
ISIS-FXI <sub>Rx</sub>	Clotting Disorders	Factor XI					
ISIS-APOCIII <sub>Rx</sub>	High Triglycerides	apoC-III					
METABOLIC							
ISIS 113715	Diabetes	PTP-1B					
ISIS-GCGR <sub>Rx</sub>	Diabetes	GCGR					
ISIS-GCCR <sub>Rx</sub>	Diabetes	GCCR					
ISIS-SGLT2 <sub>Rx</sub>	Diabetes	SGLT2					
CANCER							
OGX-011	Cancer	clusterin					TEVA OncoGeneX™ Lilly
LY2181308	Cancer	survivin					
ISIS-EIF4E <sub>Rx</sub>	Cancer	eIF-4E					OncoGeneX™
OGX-427	Cancer	Hsp27					
NEURODEGENERATIVE							
ISIS-SOD1 <sub>Rx</sub>	ALS	SOD1					
ISIS-SMN <sub>Rx</sub>	Spinal Muscular Atrophy	SMN2					
INFLAMMATION & OTHER							
Alicaforsen	Ulcerative Colitis	ICAM-1					Atlantic
ATL1102	MS	VLA-4					antisense
AIR645	Asthma	IL-4Ra					ALTAIR
Vitravene®	CMV Retinitis	CMV					NOVARTIS
ACHN-490	Severe Bacterial Infection	Aminoglycoside					ACHAAGEN
iCo-007	Ocular Disease	C-raf kinase					iCo Therapeutics Inc.
ATL1103	Acromegaly	GHr					antisense
EXC 001	Local Fibrosis	Fibrosis					EXCALIARD

# Isis' Drug Discovery & Development Programs





# Today - Isis Leads the Way in RNA Therapeutics

## ✦ Most Advanced RNA Therapeutics Company in the World

- One approved drug - Vitravene®
- Positive Phase 3 - Mipomersen
- Largest RNA pipeline - 22 drugs in development
- Broadest RNA pipeline - >5 therapeutic areas
- Most balanced RNA pipeline - preclinical to Phase 3; acute & chronic diseases; local & systemic administration

## ✦ Broadest Association with Industry-Leading Companies

- Pharmaceutical Companies
  - BMS; Genzyme; GSK; Lilly; Novartis
- Satellite Companies
  - Achaogen; Alnylam; Altair; Archemix; ATL; Atlantic; Excaliard; Ibis; iCo; OncoGenex; Regulus

## ✦ Dominant Patent Estate in RNA Therapeutics

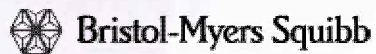
- ~1,600 issued patents worldwide
- Control antisense therapeutics
- Create formidable barriers to entry worldwide

# Key Recent Accomplishments

## Partnership Successes



➤ GSK 'Preferred Partner' Alliance



➤ BMS Milestone Payment for PCSK9



➤ Single-stranded RNA Collaboration with Alnylam



➤ Ibis Purchase by Abbott



➤ Regulus Expanded GSK Collaboration- miR-122



➤ OncoGenex License of OGX-011 to Teva

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>\$270 M

2009-2010

## Business Model at Work

### ✦ Strong Balance Sheet

- Ended first quarter with \$519M in cash
  - *Not including GSK's \$35M upfront payment*
  - *Not including Regulus' cash of \$30.7M*
- Projecting to end 2010 with >\$425M in cash

### ✦ Strong Operating Results

- First quarter pro forma NOL of \$1.5M
- Projecting 2010 pro forma NOL in mid \$50M range

### ✦ On track to exceed our EOY cash guidance & to achieve an NOL more favorable than guidance

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*Over the past three years, we have generated over \$650M in cash demonstrating that our business strategy is working*