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Nile Therapeutics, Inc. (NLTX-NASDAQ)

UPDATE

NLTX: Expect Top-Line Data From Phase II Program With CD-NP In The Q3-2010…

Current Recommendation	**Outperform**
Prior Recommendation	N/A
Date of Last Change	01/26/2010
Current Price (05/14/10)	$0.61
Target Price	**$2.00**

Nile is developing CD-NP, a chimeric natriuretic peptide currently in phase II clinical studies for the treatment of acute decompensated heart failure (ADHF). Prior phase I and phase II data so far has been highly encouraging. With a market capitalization of only $22 million, Nile Therapeutics shares are significantly under-valued.

We believe with positive data from the ongoing phase II program in hand the company is worth at least $80 to 100 million. Taking the mid-range at $90 million, and then backing out the $20 million most likely required to fund the phase IIb program, we arrive at a value of $70 million for Nile Therapeutics. This equates to a price of $2.00 per share.

SUMMARY DATA

52-Week High	**$2.16**
52-Week Low	**$0.46**
One-Year Return (%)	**16.69**
Beta	**1.57**
Average Daily Volume (sh)	**174,370**
Shares Outstanding (mil)	**27**
Market Capitalization ($mil)	**$15**
Short Interest Ratio (days)	**0.45**
Institutional Ownership (%)	**20**
Insider Ownership (%)	**28**
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 2009 Estimate	**N/A**
P/E using 2010 Estimate	**N/A**
Zacks Rank	**2**

Risk Level	**Above Average**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**
Zacks Rank in Industry	**67 of 132**

ZACKS ESTIMATES

Revenue
(In millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2009	0 A	0 A	0 A	0 A	0 A
2010	0 A	0 E	0 E	0 E	0 E
2011					10.0 E
2012					20.0 E

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

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2009	-$0.07 A	-$0.10 A	-$0.08 A	-$0.06 A	-$0.31 A
2010	-$0.07 A	-$0.06 E	-$0.05 E	-$0.06 E	-$0.24 E
2011					-$0.01 E
2012					$0.13 E

Zacks Projected EPS Growth Rate - Next 4 Years % **N/A**

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WHAT'S NEW

Financial Results…

On May 14, 2010, Nile Therapeutics reported financial results for the first quarter 2010. Nile reported no revenues for the quarter. Net loss for the quarter totaled $1.9 million, or $0.07 per diluted share. Both revenues and net loss were in-line with our expectations for the first quarter. Nile exited the first quarter ended March 31, 2010 with roughly $2.0 million in cash and investments.

In April 2010, Nile Therapeutics offered 6.5 million units of securities in an underwritten public offering for $0.70 per unit. Each unit consists of one share of NLTX common stock and 0.3 warrants to purchase common stock at anytime over the next five years for $0.94 per share. The warrants began trading on the Nasdaq Capital Market under the symbol NLTXW. In May 2010, Nile announced that underwriters have exercised their option to offer an additional 975k units, bringing the total size of the offering to 7.475 million units. Through the offering, Nile Therapeutics raised approximately $4.5 million in net proceeds. We believe this is sufficient cash to fully fund the ongoing phase II program, and provide enough cash runway to allow management to present the full data in the fourth quarter 2010 and strike a developmental partnership for CD-NP in late 2010 or early 2011.

Phase II CD-NP Program Progressing On Plan…

In May 2010, Nile Therapeutics noted that dose escalation in the ongoing phase II study (NIL-CDNP-CT005) has been completed, with management identifying a maximum tolerated dose (MTD) and two doses that appear to have an attractive safety and activity profile in patients with acute heart failure. We believe these are the 1.25ng and 2.5ng/kg/min doses. So far there has been no substantial risk of hypotension in these cohorts. Management is now pushing forward with additional dose cohorts, which we suspect include 3.75ng, 5ng, and 10ng/kg/min. As of May 12, 2010, 57 of the total 75 patients have been enrolled in the program in U.S., Germany, and Israel.

We are expecting to see top-line data from this program in the third quarter 2010, with full data to be presented at the end of the year. The net $4.5 million cash raised in May 2010 allows for management to complete this program, present the data, and continue discussions with potential partners into 2011.

The development plan is to move into a larger-scale phase IIb program during 2011. We expect this program to enroll roughly 300 patients. We expect that management will seek to meet with the U.S. FDA to finalize the endpoints for this program following the analysis of the current phase II trial. We expect these endpoints to include relief of symptomatic dyspnea, as well as analysis of biomarkers for kidney function and ischemia, as well as safety assessments including risk of hypotension, renal function, cardiovascular events, and mortality. The cost of this planned phase IIb program is estimated to be between $15 and $20 million. Therefore, management must secure financing for this phase IIb program before it begins through a developmental partnership with a larger pharmaceutical company.

Staying Positive

We see a significant market opportunity for CD-NP. There are an estimated 1.2 million hospitalizations each year in the U.S. with the primary admission cause of acute decompensated heart failure (ADHF). Nearly three-quarters of these patients also have stage II or stage III chronic kidney disease (CKD). The majority (~75%) present with a systolic blood pressure (SBP) above 120 mmHg and would be eligible for treatment with a vasodilator. A product specifically indicated for the treatment of patients with ADHF with mild to moderate CKD, which is safe to use on top of Lasix, could have significant sales potential.

We think if CD-NP can demonstrate effectiveness in the planned phase IIb, Nile can fetch at least $300 million on a takeover in 2011 or 2012. However, shareholders may not have to wait that long to reap their rewards. Our expectation is that management will look to secure funding from a partner after the phase II data comes out later this year. We could be looking at an upfront payment plus potential takeover milestones in 2011. What is clear to us is that with a market capitalization of only $22 million, Nile Therapeutics shares are significantly under-valued. We believe with positive data in hand, the company is worth at least $80 to 100 million. Taking the mid-range at $90 million, and then backing out the $20 million most likely required to fund the phase IIb program, we arrive at a value of $70 million for Nile Therapeutics. This equates to a price of $2.00 per share.

OVERVIEW

Nile Therapeutics is a development stage biopharmaceutical company in the business of commercially developing innovative products for the treatment of cardiovascular diseases. The lead compound is CD-NP, a chimeric natriuretic peptide currently in phase II clinical studies for the treatment of acute decompensated heart failure, or ADHF. However, CD-NP may be useful in several other cardiovascular and renal indications. The company also is developing CU-NP, a pre-clinical rationally designed natriuretic peptide that consists of amino acid chains identical to those produced by the human body, specifically the ring structure of C-type natriuretic peptide, or CNP, and the N- and C-termini of Urodilatin, or URO. The company is headquartered in San Mateo, CA.



Heart Failure

Heart Failure (HF) can be a chronic or acute condition in which the structure of function of the heart impairs its ability to supply sufficient blood flow to meet the body's needs. The most common manifestation of the disease is low cardiac output (known as congestive heart failure). HF is most commonly caused by an acute myocardial infarction (heart attack), ischemic heart disease, hypertension, valvular heart disease, or cardiomyopathy. These can cause impairment to the contractility (systolic heart failure) or impairment to relaxation and ventricular filling (diastolic heart failure). The most common cause of heart failure is left ventricular systolic dysfunction. Dysfunction is defined as an ejection fraction of 50% or less, or a categorical assessment of moderately or severely impaired.

According to data from the National Health and Nutrition Examination Survey (NHANES I), a 19-year, 13,000 patient retrospective analysis, risk of developing HF is associated with the following underlying conditions:

Underlying Condition	Risk of HF
…Ischaemic Heart Disease	62%
…Cigarette Smoking	16%
…Hypertension	10%
…Obesity	8%
…Diabetes	3%
…Valvular Disease	2%

According to the Acute Decompensated Heart Failure National Registry (ADHERE), a 10-year observational registry of the management of 200,000 patients treated in 280 hospitals for HF, common co-morbid conditions that must be considered during treatment include:

Co-Morbid Condition	Frequency
…Hypertension	73%
…Coronary Artery Disease	57%
…Diabetes	44%
…Atrial Fibrillation	31%
…Asthma / COPD	31%
…Chronic Renal Insufficiency	30%

Acute decompensated heart failure (ADHF) is the sudden onset of heart failure, and can lead to severe consequences, including acute respiratory distress. Symptoms include shortness of breath (dyspnea), coughing, ankle swelling, and reduced exercise capacity. The dyspnea is generally associated with rapid accumulation of fluid within the lung's interstitial and alveolar spaces, which is the result of acutely elevated cardiac filling pressures (cardiogenic pulmonary edema). Heart failure is also associated with significantly reduced physical and mental health, resulting in a markedly decreased quality of life. Renal insufficiency (kidney failure) is also often common in patients with ADHF. In fact, over the past several years, it has become apparent that the interaction between the heart and the kidneys plays a critical role in the progression of heart failure. Generally speaking, worsening stages of chronic kidney disease (CKD) are associated with longer hospital stays and higher mortality rates in patients with acute heart failure.

…Epidemiology…

In the U.S., approximately 5.5 million people (~2% of the population) suffer from heart failure. The incidence is even higher for patients above the age of 65, where approximately 6% to 10% of the population is at risk. There are an estimated 650,000 new cases diagnosed annually.

Treatment of heart failure generates annual costs of approximately $35 billion, of which approximately $3 billion is spent on drugs and $19 billion is spent in the acute hospital setting. HF patients frequently suffer acute episodes of decompensated heart failure (ADHF) which require hospitalization. Each year, HF is responsible for over 1.2 million hospitalizations. For Americans over the age of 65, ADHF is the most frequent cause of hospital admission, and the incidence has doubled in the past 25 years. The average length of hospital stay is 4.3 days. Subsequent to a discharge for ADHF, the average time to re-admission is 3 months and mortality is high. In fact, 50% of patients discharged with a primary or secondary code of ADHF will require re-hospitalization during the following 9 months.

Period Following Hospitalization	Mortality Rate
…1 Month	12%
…12 Months	33%
…5 Years	50%

According to the ADHERE Registry, mortality rates are higher for patients with elevated blood urea nitrogen (BUN), low systolic blood pressure (SBP), and high serum creatinine (SCr). Data from the ADHERE study demonstrates that elevated BUN is the single strongest predictor of in-hospital mortality in patients admitted with ADHF. The BUN test is a measure of the amount of nitrogen in the blood in the form of urea, and a measurement of kidney function. Urea is a substance secreted by the liver, and removed from the blood by the kidneys.

Vital Signs		Mortality Rate
…Blood Urea Nitrogen (BUN)	≥ 43mg/dL	▼
	≤ 43mg/dL	▲
…Serum Creatinine Levels (SCr)	≥ 2.75 mg/dL	▲
	≤ 2.75 mg/dL	▼
…Systolic Blood Pressure (SBP)	≥ 115 mm Hg	▲
	≤ 115 mm Hg	▼

Chronic kidney disease (CKD) is identified by a blood test for creatinine and BUN. Creatinine, normally produced by the body at a fairly constant rate, is a break-down waste product of creatine phosphate in muscle. It is chiefly filtered out of the blood by the kidneys, though a small amount is actively secreted by the kidneys into the urine. Therefore, if the filtering of the kidney is deficient, e.g. in kidney failure, blood levels for both urea and creatinine rise. Glomerular filtration rate (GFR) describes the flow rate of filtered fluid through the kidney. Lower GFR indicates a failing kidney with decreased capability to excrete waste products. Creatinine levels may be normal in the early stages of CKD, but increase in time as the disease worsens. As such, creatinine clearance, reflected by the GFR, is a clinically important measurement of renal function.

Prevalence and severity of renal dysfunction in patients with ADHF, along with mortality rate, demonstrates the relationship between worsening kidney function and heart failure:

CKD Severity	Prevalence	In-Hospital Mortality Rate
Stage I *(GFR > 90)*	Male = 11%	1.9%
	Female = 8%	
Stage II *(GFR 60 - 90)*	Male = 30%	2.3%
	Female = 25%	
Stage III *(GFR 30 - 60)*	Male = 41%	3.9%
	Female = 46%	
Stage IV *(GFR 15 - 30)*	Male = 12%	7.6%
	Female = 15%	
Stage V *(GFR < 15)*	Male = 7%	6.5%
	Female = 7%	

Source: Journal of Cardiac Failure Vol. 13 No. 6 August 2007

It is clear that patients with worsening renal function during hospitalization for heart failure are associated with higher unfavorable outcomes. As noted above, and confirmed by Haywood et al in the Journal of Cardiac Failure (Vol. 13 No. 6 August 2007), BUN is the single strongest predictor of inpatient mortality. However, GFR provides a more accurate estimation of renal function and better quantifies the degree of renal impairment. Therefore, calculating both GFR and BUN provides complementary information that can be used as a prognostic tool for predicting patient outcomes during hospitalization with ADHF. Accordingly, when looking for an ideal treatment option for a patient presenting to the hospital with ADHF, the following characteristics should be considered:

Clinical Profile	Ideal Drug
Diuretic & Natriuretic	✓
Preserve / Enhance Renal Function	✓
Reduce Cardiac Filling Pressure	✓
Low Risk of Hypotension	✓

…Treatment Options…

Treatment of HF includes a combination of vasodilators, diuretics, and non-invasive positive pressure ventilation (NIPPV). Other treatment options also include a mixture of pharmaceutical products, including ACE inhibitors, angiotensin receptor blockers (ARBs), Beta-blockers, inotropic agents, and surgery.

- Vasodilators: Vasodilation refers to the widening of blood vessels resulting from relaxation of smooth muscle cells within the vessel walls, particularly in the large arteries, smaller arterioles and large veins. When vessels dilate, the flow of blood is increased due to a decrease in vascular resistance. The resulting dilation leads to a decrease in blood pressure. Vasodilators include nitrates such as nitroglycerin and nitroprusside. The body converts the nitroglycerin into nitric oxide, a messenger molecule that tells the smooth muscles of the surrounding blood vessels to relax. Nitro comes in sublingual tablets and sprays for short-acting (acute) heart failure, or patches for long-acting (chronic) heart failure. Physicians have been using nitro efficacy for the treatment of angina and heart attack for over 100 years. However, these drugs do very little to preserve renal function and patients must be monitored while on the drug for risk of hypotension (low blood pressure). Side effects include severe headaches, dizziness, and tachycardia. The body also develops a tolerance to nitro, leading to a resistance to its vasodilating effects. The body can also experience withdrawal symptoms following long-term use. This makes the drug a rather poor choice for patients with chronic heart failure.

- Diuretics: A diuretic is any drug that elevates the rate of urination and provides a means for reducing fluid retention. Commonly used diuretics include furosemide and metolazone. Furosemide (sold branded by Sanofi-Aventis as Lasix) is a loop diuretic. The drug acts by inhibiting the body's ability to reabsorb sodium at the ascending loop in the kidney. This leads to retention of water in the urine. The effects of Lasix are roughly six hours ("last-six"). Overuse can cause dehydration, electrolyte imbalance, metabolic alkalosis, seizures, and renal damage. Metolazone is a thiazide diuretic that indirectly decreases the amount of water reabsorbed into the bloodstream by the kidney, so that blood volume decreases and urine volume increases. It his lowers blood pressure and prevents excess fluid accumulation in heart failure. Metolazone is commonly used in combination with furosemide. This causes effective diuresis, but can often lead to significant electrolyte abnormalities, hyponatremia (low sodium), hypokalemia (low potassium), hypercalcemia (high calcium), and hyperuricemia (high uric acid). Side effects include dizziness, headache, and heart palpitations.

- Inotropes: Inotropic agents alter the force of energy of muscular contractions by manipulating calcium levels in the cytoplasm. There are two types of inotropic agents, negative agents that weaken muscle contraction by decreasing calcium and positive agents that strengthen muscle contraction by increasing calcium. The choice largely depends on specific pharmacological effects of individual agents with respect to the condition. Positive inotropic agents increase myocardial contractility, and are used to support cardiac function in conditions such as ADHF, myocardial infarction, and cardiomyopathy. Commonly used positive inotropic agents for the treatment of heart failure include milrinone, dobutamine, and levosimedan. Milrinone is a phosphodiesterase III inhibitor that increases the effects of cyclic adenosine monophosphate (cAMP) and enhances relaxation of the left ventricle by increasing calcium uptake. It is primarily used with when vasodilating and diuretic agents are insufficient. However, ventricular arrhythmia is a potential serious side effect and limits more widespread use. Levosimendan is a calcium sensitizer that increased the sensitivity of the heart to calcium and facilitates cardiac contractility without actually having to intracellular calcium levels. The drug also has mild vasodilating properties. Unfortunately, the drug is contraindicated in patients with moderate-to-severe renal impairment, and thus not a good option for broad-scale use. Dobutamine is a direct-acting agent that stimulates the beta-1-adrenoceptors of the heart, thus increasing contractility and cardiac output. Both dobutamine and levosimedan are associated with tachycardia and hypertension.

- VAD: A ventricular assist device ("VAD") is a mechanical circulatory device that is used to partially or completely replace the function of a failing heart. They can be used over the short-term when patients are recovering from a heart attack or heart surgery, or can be implanted for long-term use in patients with congestive heart failure (that require a transplant). VADs are divided into two main categories: pulsatile pumps, that mimic the natural pulsing action of the heart, and continuous flow pumps. Retrospective analysis demonstrates that use of left ventricular VAD result in improved cardiac and metabolic function, less renal failure, and significant higher event-free survival rates that inotropic agents. However, because the devices generally result in blood flowing over a non biologic surface, predisposing the blood to clotting, there is need for continuous anticoagulation measures.

…Along Comes Natrecor…

In August 2001, a small biotechnology company, Scios Inc., received approval for what, at the time, was considered to be a major breakthrough for the treatment of ADHF with Natrecor (nesiritide). Nesiritide is the recombinant form of the 32 amino acid human B-type natriuretic peptide (BNP), which is normally produced by the ventricular myocardium. Nesiritide works to facilitate cardiovascular fluid homeostasis through counter-regulation of the renin-angiotensin-aldoesterone system, stimulating cyclic guanosine monophosphate, leading to smooth muscle cell relaxation. The product was believed to provide all of the vasodilating characteristics of nitroglycerine, with the diuretic and natriuretic properties of furosemide, while also reducing cardiac filling pressure. This was virtually a homerun in terms of treating patients with ADHF, as long as the risk of hypotension (low blood pressure) could be effectively managed. Scios was later acquired by large-cap pharmaceutical company, Johnson & Johnson, in 2003 for $2.4 billion in cash. At the time the deal valued Scios at over 50x Natrecor's revenue.

Natrecor sales were annualizing over $400 million in 2004 and were on schedule to be the billion-dollar blockbuster J&J had anticipated. Unfortunately, in 2005, a meta-analysis of patient outcomes on Natrecor painted a very different profile than the drugs proposed mechanism. Use of Natrecor was identified with increased mortality and increased renal dysfunction compared to the standard of care. Natrecor was thought to increase GFR by causing dilation of the afferent renal arterioles and constriction of the efferent renal arterioles. BNP stimulation also leads to relaxation of renal mesangial cells, increasing the surface area for filtration, thus further increasing GFR. Unfortunately, there were significant indirect effects that actually lead to a decrease in GFR (worsening in renal function) in the real world setting. BNP, a rather potent vasodilator, lowers systemic blood pressure (SBP), decreasing renal blood flow and hence decreasing GFR. In addition, BNP inhibits angiotensin II production. Angiotensin II normally causes constriction of the efferent renal arterioles (increasing GFR). Inhibition of angiotensin II results in a decreased GFR.

In June 2005, the U.S. FDA and J&J issued a "Dear Doctor" letter reminding physicians that, "Nesiritide should be strictly limited to patients presenting to the hospital with acutely decompensated heart failure who have dyspnea at rest." The warning also urged physicians to consider the possible risks of the drug, and the availability of alternate therapies to relieve the symptoms of congestive heart failure. The warning finally notes that nesiritide should not be used for intermittent outpatient infusion, for scheduled repetitive use, to improve renal function, or to enhance diuresis. This was a significant blow to the sales prospect of the drug. Some even lobbied for the drugs withdrawal from the market. Sales of Natrecor in 2008 were only $64 million.

…A Wide Open Market…

The rise and fall of Natrecor sent physicians back almost a decade in treating ADHF. Natrecor's was headed towards blockbuster sales before the meta-analysis ended the run. Nitroglycerin and furosemide returned as the standards of care despite significant limitations. In our view, the market for an effective product is wide open. The objectives are simple, increase cardiac output while offloading fluid and preserving renal function. An effective product with the target profile listed below is sure to offer blockbuster potential.

Clinical Profile	Ideal Drug	Lasix	Nitro	Inotropes	Natrecor
Diuretic & Natriuretic	✓	✓	-	-	-
Preserve / Enhance Renal Function	✓	✗	-	✗	✗
Reduce Cardiac Filling Pressure	✓	✓	✓	✓	✓
Low Risk of Hypotension	✓	✓	✗	✓	-

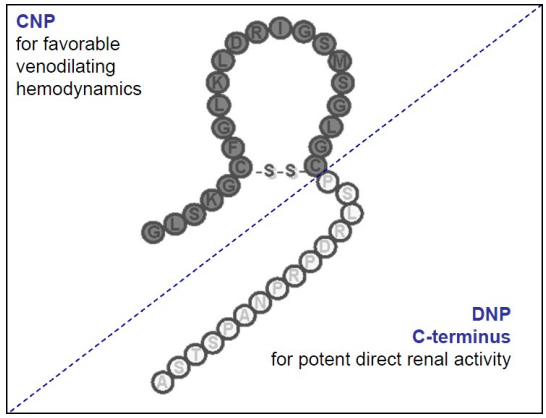
CD-NP

Nile Therapeutics is developing CD-NP, a chimeric natriuretic peptide currently in phase II clinical studies for the treatment of acute decompensated heart failure (ADHF). Although, management believes the drug may have utility in other indications which include preservation of cardiac function subsequent to acute myocardial infarction, or AMI, and prevention of renal damage subsequent to cardiac surgery.

CD-NP was rationally designed by scientists at the Mayo Clinic's cardio-renal research labs. CD-NP was designed to preserve the favorable effects of current therapies while eliminating or attenuating the hypotensive response, and enhancing or preserving renal function. Natriuretic peptides are naturally occurring proteins produced in the heart and blood vessels that cause natriuresis (the removal of sodium and water from the blood). There are four naturally produced natriuretic peptides: atria "A-type" natriuretic peptide (ANP), brain "B-type" natriuretic peptide (BNP), cell "C-type" natriuretic peptide, (CNP), and dendroaspis "D-type" natriuretic peptide (DNP). These peptides possess potent natriuretic, diuretic, and vasodilating activities and are implicated in body fluid homeostasis and blood pressure control. Unlike ANP, BNP and DNP, CNP does not have direct natriuretic activity. This is because CNP is a selective agonist for the B-type natriuretic receptor (NPR_B) whereas ANP, BNP and DNP are selective for NPR_A. ANP, BNP and DNP have potent arteriodilation effects, whereas CNP has venodilation effects. ANP and BNP have direct renal effects offset by reduced renal perfusion. DNP, on the other hand is potent direct renal activator. CNP has no known renal effects.

Natriuretic Peptides	Receptor Target	Hemodynamic Effects	Renal Effects
ANP 	NPR_A	Arteriodilation	Renal Effects Offset by Reduce Perfusion
BNP 	NPR_A	Arteriodilation	Renal Effects Offset by Reduce Perfusion
CNP 	NPR_B	Venodilation	None
DNP 	NPR_A	Arteriodilation	Potent Direct Renal Activator

Niles' CD-NP is a combination of two natriuretic peptides, CNP and DNP. The scientists at the Mayo Clinic developed the drug combining the n-terminus of the CNP molecule, preserving the favorable venodilating and hemodynamic properties of the molecule, with the c-terminus of the DNP molecule, preserving the potent direct renal activity. Preclinical data demonstrates the drug has both natriuretic and diuretic properties. Animal studies yielded very encouraging data with respect to improvement in GFR (improvement in renal function) and less risk of hypotension as compared to BNP. Preclinical data on the mechanism of action was published in the Journal of the American College of Cardiology (ACC), Vol. 52, No. 1, 2008.



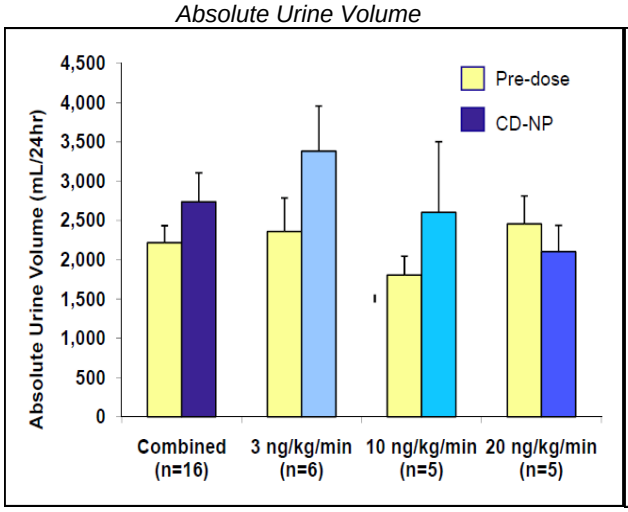
…Phase I & II Data…

In 2007, Nile conducted a phase Ia program in 22 healthy volunteers with a 4 hour IV infusion of CD-NP. The trial included an open-label dose-escalation cohort (10, 17.5, 25 ng/kg/min) and a double-blind cohort vs. placebo at the 17.5 ng/kg/min dose. Results demonstrated safety, as well as natriuretic and diuretic actions with preservation of GFR and minimal hypotension risk. Nile then conducted a phase Ib open-label dose escalating program in 20 patients with heart failure and evidence of intravascular volume (fluid) overload. The program assessed the pharmacodynamic, hemodynamic, and renal effects of a 24-hour IV infusion of CD-NP. Results demonstrated:

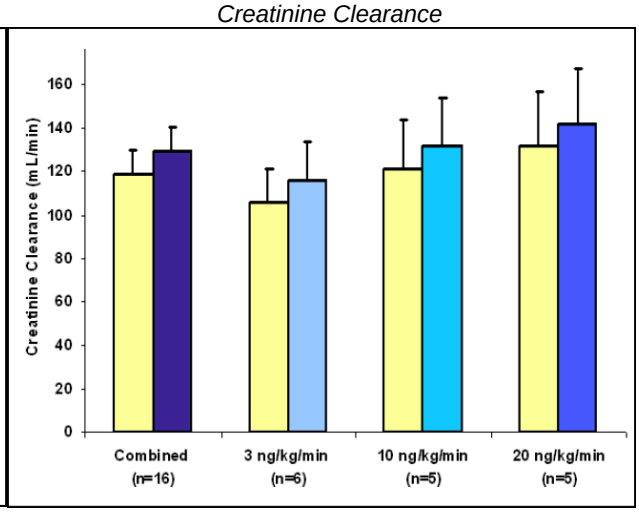
- ✓ CD-NP was well tolerated at doses up to 20 ng/kg/min
- ✓ A statistically significant reduction in serum creatinine
- ✓ A statistically significant increase in creatinine clearance
- ✓ Diuresis similar to Lasix
- ✓ Blood pressure effects were dose dependent and well characterized.

CD-NP vs. Lasix

Absolute Urine Volume



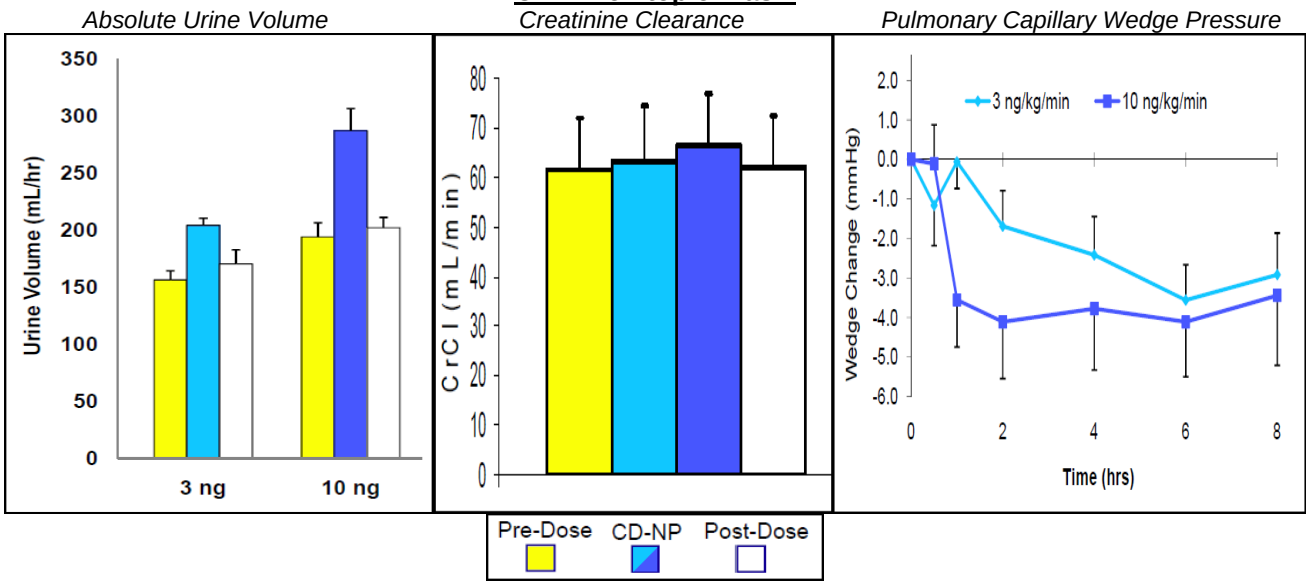
Creatinine Clearance



The encouraging phase Ib data was follow-up by a phase IIa program initiated in July 2008 testing the proof-of-concept in 23 patients with "stabilized" acute heart failure. The trial was designed to assess the hemodynamic effects of CD-NP on patients with stabilized AHF in an open-label, dose escalating format. Patients received two 8 hour IV infusions of CD-NP, separated by a 14 hour washout period, on top of existing Lasix therapy. Preliminary top-line results were released demonstrated:

- ✓ A reduction in pulmonary capillary wedge pressure (PCWP)
- ✓ An increase in diuresis
- ✓ No symptomatic hypotension
- ✓ No observed change in renal function
- ✓ Dose response from the 3 to 10 ng/kg/min level

CD-NP on top of Lasix



There were no drug-related serious adverse events in the phase Ib or phase IIa program. Management identified the maximum tolerated dose (MTD) at 30 ng/kg/min (symptomatic hypotension). In our view, the clinical program so far has been very astutely designed to assess the clinical effects of the drug. The phase Ia program studied the drug in healthy patients. The phase Ib moved dosing into patients with acute heart failure that has been stable for at least the past six months. In the phase IIa program, management tested CD-NP in patients with acute heart failure that have been stable for at least the past 24 hours. All the while the safety, pharmacokinetics and pharmacodynamics of the drug were being analyzed to plan for the larger phase II program.

…Current Phase II Program…

In June 2009, Nile initiated a phase II open-label, single-blind, placebo-control program designed to determine a safe and tolerable dose range of CD-NP that can be used in ADHF patients in the acute (presenting to the hospital) setting in combination with the standard of care (furosemide + vasoactive or inotropic agents). The study also contains several exploratory efficacy endpoints to provide insight into the potential for CD-NP to preserve or enhance renal function in acute heart failure patients.

→ Kidney function will be measured during infusion, at day 5, 14, and 30 using creatinine and cystatin-c (a heart failure specific kidney function biomarker).
→ Dyspnea will also be measured at 6, 24, and 72 hours using the Likert Scale.
→ Other data points include urine volume and ischemic biomarkers such as Ngal and KIM-1.
→ Safety assessments include risk of hypotension, renal function, use of furosemide rescue medication, cardiovascular events, and mortality.

The study was initially designed to enroll up to approximately 40 patients in 3 dose cohorts (1.25ng, 2.5ng, and 5ng/kg.min) of CD-NP over a 48 to 72-hour infusion. In the study, the dosage of CD-NP was to be increased in successive cohorts to assess the dose relationship of CD-NP on improvement of clinical symptoms and renal function in ADHF patients. However, after dosing 7 subjects in the first cohort, four of whom received CD-NP at a dose level of 5 ng/kg/min and three of whom received placebo, Nile suspended enrollment of the study because the average blood pressure decrease in both the placebo and CD-NP patients was larger than predicted.

Management believes the greater than predicted response may have originated from the timing and quantity of concomitant medications (furosemide, nitro, etc…) versus study drug in the acute setting, as well as from the inclusion of patients who were more susceptible to risks from blood pressure deviations. It is important to know that ADHF patients often arrive at the hospital heavily medicated. Patients may be on oral medications including beta blockers, ACE inhibitors, anti-clotting agents, alpha blockers or statins. Physcians need to be careful when, and how much, of any vasoactive drug they administer. Care must be taken to make sure patients are not hypotensive prior to IV dosing of standard. There is normally a drop in blood pressure following administration of furosemide, but the magnitude is manageable. It seems as though dosing CD-NP immediately following furosemide presents too great a hypotensive risk given the nature of the patient.

Therefore, management submitted to the FDA a protocol amendment to (1) modify the exclusion criteria relating to the timing and quantity of bolus IV furosemide administration acceptable in the first 24 hours upon hospital admission, (2) provide additional guidance on the concomitant use of vasoactive oral and IV medication, (3) increase the entry blood pressure range, and (4) add additional dose levels to be studied.

Following the FDA's approval of the amended protocol, Nile began enrolling subjects in the 2nd and 3rd cohorts. As of March 12, 2010, enrollment is complete in the 1.25 ng/kg/min and 2.5ng/kg/min cohorts, with no substantial risk of hypotension evident. Management believes it has identified two doses that appear to have an attractive safety and activity profile in patients with acute heart failure and a maximum tolerated dose (MTD). We believe management will continue to test doses ranging from 3.75ng/kg/min up to 10ng/kg/min. As of May 12, 2010, 57 of the planned 75 patients have been enrolled. We expect top-line data late in the third quarter, and full results by the end of the year.

…Commercialization Plans…

Following the completion of the phase II program discussed above, we believe the company will look to secure a development partnership for the next wave of clinical programs. This is expected to include a phase IIb program in roughly 300 patients. We expect that management will seek to meet with the U.S. FDA to finalize the endpoints following the analysis of the current phase II trial. If management cannot secure a partnership on the above phase II data alone, we may see an interim cash raise in the third quarter. The cost of the phase IIb program is estimated at around $15 to 20 million. Nile, along with its partner, will need to conduct two phase III programs, one focusing on efficacy (dyspnea, kidney function biomarkers, cardiac output) and another focusing on safety (risk of hypotension, cardiovascular events, mortality). If these trials are completed on schedule, the duo should be in position to file a new drug application (NDA) around the middle of 2013, putting U.S. FDA action on CD-NP in 2014.

As noted above, there is a significant market opportunity for CD-NP. There are an estimated 1.2 million hospitalizations each year in the U.S. with the primary admission cause of acute decompensated heart failure (ADHF). Nearly three-quarters of these patients also have stage II or stage III chronic kidney disease (CKD). The majority (~75%) present with a systolic blood pressure (SBP) above 120 mmHg and would be eligible for treatment with a vasodilator. A product specifically indicated for the treatment of patients with ADHF with mild to moderate CKD, which is safe to use on top of Lasix, could have significant sales potential. The target profile is clear: improve dyspnea, remove excess fluid volume, and preserve kidney function. Do this, and there are at least 650k patients each year that could use the drug. The opportunity outside the U.S. is equally as attractive. We think that makes CD-NP a potential $500 million + product within a few years after launch. In addition to Nile's current clinical program in ADHF, the mechanism of CD-NP presents an opportunity to develop the molecule in other indications, including preservation of cardiac function subsequent to acute myocardial infarction (AMI), and preservation of renal damage subsequent to cardiac surgery.

…Taking a Stab at Partnership Terms…

There are three deals we are using as a basis for predicting what a potential partnership between Nile Therapeutics and a larger or specialty pharmaceutical company on CD-NP could look like:

- J&J acquires Scios for $2.4 billion in February 2003. J&J paid a very hefty premium for Scios and Natrecor back in 2003. At the time of the deal close, Natrecor had trailing twelve-month sales of only $50 million. However, the trajectory was straight up, and J&J had hopes that Natrecor was going to be a blockbuster. We note that J&J has not given up on Natrecor however. The company is current conducting a massive, 10,000 patient outcome study over a four year period with Natrecor called ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure). ASCEND-HF is a testing lower doses of Natrecor with the goal to show reduced mortality. It began in September 2006 and should complete later this year.

- Merck acquires NovaCardia for $350 million in July 2007: Valuing Merck's purchase of NovaCardia is a little difficult because the company was privately-held at the time of the deal. NovaCardia's lead product candidate, rolofylline (MK-7418), was an adenosine A1 receptor antagonist in phase III clinical trials in patients with acute congestive heart failure (CHF). KW-3902 was believed to block adenosine-mediated constriction of blood flow to the kidneys and inhibit reabsorption of salt and water by the kidney, thereby increasing urine volume and maintaining renal function in patients with CHF. Merck believed they would be first to market with a vasodilator that demonstrated that helps preserve renal function. Unfortunately for Merck, the drug failed its phase III program (PROTECT-1 and PROTECT-2) and future development is on hold.

- Novartis acquires Corthera for $120 million in December 2009: Novartis scooped up Corthera, and its phase III candidate, relaxin, for the potential treatment of acute decompensated heart failure (ADHF) in late 2009. Relaxin, a naturally occurring hormone, is a potent vasodilator, which has shown in previous clinical trials to increase cardiac output after a 48-hour infusion post hospitalization for ADHF. The $120 million seems like a steal for Novartis until you factor in the potential $500 million in future milestones the company could still owe to Corthera shareholders upon successful commercialization of the drug.

It is clear that a post phase II candidate in this space is worth at least $350 million. However, given the failures of the Merck deal, and what happened with Natrecor at J&J, we are not surprised at all to see Novartis acquire Corthera with a heavily back-end loaded milestone format. Over the past year we are starting to see more and more pharma-biotech deals taking this upfront + future cash format. If management at Nile is looking to sell the entire company, we expect a similar type deal.

The question is when Nile looks to sell or partner. Obviously the farther along the development timeline management can take CD-NP the more money they will command on the open market. Positive phase II results in the current ongoing trial probably puts the value of the program at $80 to 100 million. Not bad considering the current market capitalization is only $30 million. Positive phase IIb results in the next 330 patient program means Nile can probably sell for $300 million or higher. However, management will need to bridge that financing gap between the current phase II program and the completion of a large-scale phase IIb. The company may need to raise as much as $20 million to conduct this trial on its own.

…Preclinical Pipeline…

Besides CD-NP, Nile Therapeutics also licensed CU-NP from the Mayo Clinical. Similarly to CD-NP, CU-NP arose from the cardio-renal research labs in an attempt to create the ideal pharmaceutical candidate for the treatment of heart failure. CU-NP was designed to combine the favorable hemodynamic venodilating effects of CNP generated via NPR_B receptor agonism, with the beneficial renal effects of Urodilatin (URO) generated via NPR_A receptor agonism. In animal models, CU-NP was shown to increase natriuresis, diuresis, and glomerular filtration (GFR) rate in a dose dependent manner, decrease cardiac filling pressure, and inhibit the renin-angiotensin system without inducing significant hypotension. The company is currently working on preclinical pharmacological studies to evaluate formulations and dose levels of CU-NP for chronic administration. If feasible, Nile plans to initiate pre-clinical toxicology and manufacturing activities in 2010.

RECOMMENDATION

We see a significant market opportunity for CD-NP. There are an estimated 1.2 million hospitalizations each year in the U.S. with the primary admission cause of acute decompensated heart failure (ADHF). Nearly three-quarters of these patients also have stage II or stage III chronic kidney disease (CKD). The majority (~75%) present with a systolic blood pressure (SBP) above 120 mmHg and would be eligible for treatment with a vasodilator. A product specifically indicated for the treatment of patients with ADHF with mild to moderate CKD, which is safe to use on top of Lasix, could have significant sales potential. The target profile is clear: improve dyspnea, remove excess fluid volume, and preserve kidney function. Do this, and there are at least 650,000 patients each year that could use the drug. The opportunity outside the U.S. is equally as attractive.

Natrecor (nesiritide), a recombinant form of the 32 amino acid human B-type natriuretic peptide (BNP), entered the market in 2001. By 2004 the drug was annualizing over $400 million in revenues and on its way to $1 billion. J&J acquired Natrecor's developer, Scios, for $2.4 billion in February 2003. Natrecor was priced aggressively – roughly $10,000 for a 72-hour treatment. Generic alternatives including nitroglycerine and furosemide cost virtually nothing in comparison. At this point, estimating a price on CD-NP is a difficult task. We have yet to see the phase II data. However, phase I data and the mechanism of action are extremely promising. Even assuming a price for the drug half that of the flawed Natrecor gets us to peak sales at $500 million. And in addition to Nile's current clinical program in ADHF, the mechanism presents an opportunity to develop the molecule in other indications, including preservation of cardiac function subsequent to acute myocardial infarction (AMI), and preservation of renal damage subsequent to cardiac surgery.

We think if CD-NP can demonstrate effectiveness in the planned phase IIb, Nile can fetch at least $300 million on a takeover in 2011 or 2012. However, shareholders may not have to wait that long to reap their rewards. Our expectation is that management will look to secure funding from a partner after the phase II data comes out around the middle of this year. We could be looking at an upfront payment plus potential takeover milestones in 2011. Or management could look for an equity investment from a potential partner to conduct the phase IIb program. What is clear to us is that with a market capitalization of only $22 million, Nile Therapeutics shares are significantly under-valued. We believe with positive data in hand, the company is worth at least $80 to 100 million. Taking the mid-range at $90 million, and then backing out the $20 million most likely required to fund the phase IIb program, we arrive at a value of $70 million for Nile Therapeutics. This equates to a price of $2.00 per share.

PROJECTED FINANCIALS

Nile Therapeutics, Inc.
Income Statement

	2009 A	Q1 A	Q2 E	Q3 E	Q4 E	2010 E	2011 E	2012 E	2013 E	2014 E
CD-NP (U.S. Sales)	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-	-	-
CD-NP (Row Sales)	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-	-	-
CD-NP (Royalties)	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-	-	-	-
Grants, Licenses & Milestones	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$10.0**	**$20.0**	**$25.0**	**$25.0**
YOY Growth	-	-	-	-	-	-	*100.0%*	*100.0%*	*25.0%*	*0.0%*
Total Revenues	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$10.0**	**$20.0**	**$25.0**	**$25.0**
YOY Growth	-	-	-	-	-	-	*100.0%*	*100.0%*	*25.0%*	*0.0%*
CoGS	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	*0%*	-	-	-	-	*0.0%*	*0%*	*0%*	*0%*	*0%*
R&D	$4.5	$1.3	$1.3	$1.1	$1.4	$5.1	$7.5	$12.0	$15.0	$15.0
% R&D	-	-	-	-	-	-	*75.0%*	*60.0%*	*60.0%*	*60.0%*
SG&A	$3.4	$0.6	$0.7	$0.7	$0.8	$2.8	$3.0	$3.5	$4.5	$5.0
% SG&A	-	-	-	-	-	-	*30.0%*	*17.5%*	*18.0%*	*20.0%*
Operating Income	($7.9)	($1.9)	($2.0)	($1.8)	($2.2)	($7.9)	($0.5)	$4.5	$5.5	$5.0
Operating Margin	*0%*	-	-	-	-	*0.0%*	*-5.0%*	*22.5%*	*22.0%*	*20.0%*
Interest & Other Income	($0.1)	$0.0	$0.0	$0.1	$0.1	$0.2	$0.1	$0.3	$0.4	$0.4
Pre-Tax Income	($7.9)	($1.9)	($2.0)	($1.8)	($2.1)	($7.8)	($0.4)	$4.8	$5.9	$5.4
Taxes	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	($7.9)	($1.9)	($2.0)	($1.8)	($2.1)	($7.8)	($0.4)	$4.8	$5.9	$5.4
Net Margin	*0%*	-	-	-	-	*0.0%*	*-4.0%*	*24.0%*	*23.6%*	*21.6%*
Reported EPS	**($0.31)**	**($0.07)**	**($0.06)**	**($0.05)**	**($0.06)**	**($0.24)**	**($0.01)**	**$0.13**	**$0.16**	**$0.14**
YOY Growth	-	-	-	-	-	*-22.4%*	*-95.4%*	*-1267.6%*	*19.7%*	*-10.8%*
FAS-123R Expense	$2.2	$0.4	$0.5	$0.6	$0.6	$2.1	$2.7	$3.2	$3.6	$3.6
EPS Impact of FAS-123R	*($0.09)*	*($0.02)*	*($0.02)*	*($0.02)*	*($0.02)*	*($0.07)*	*($0.08)*	*($0.09)*	*($0.09)*	*($0.09)*
Weighted Ave. Shares Out	25.5	27.1	32.1	34.7	34.8	32.2	36.0	37.0	38.0	39.0

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

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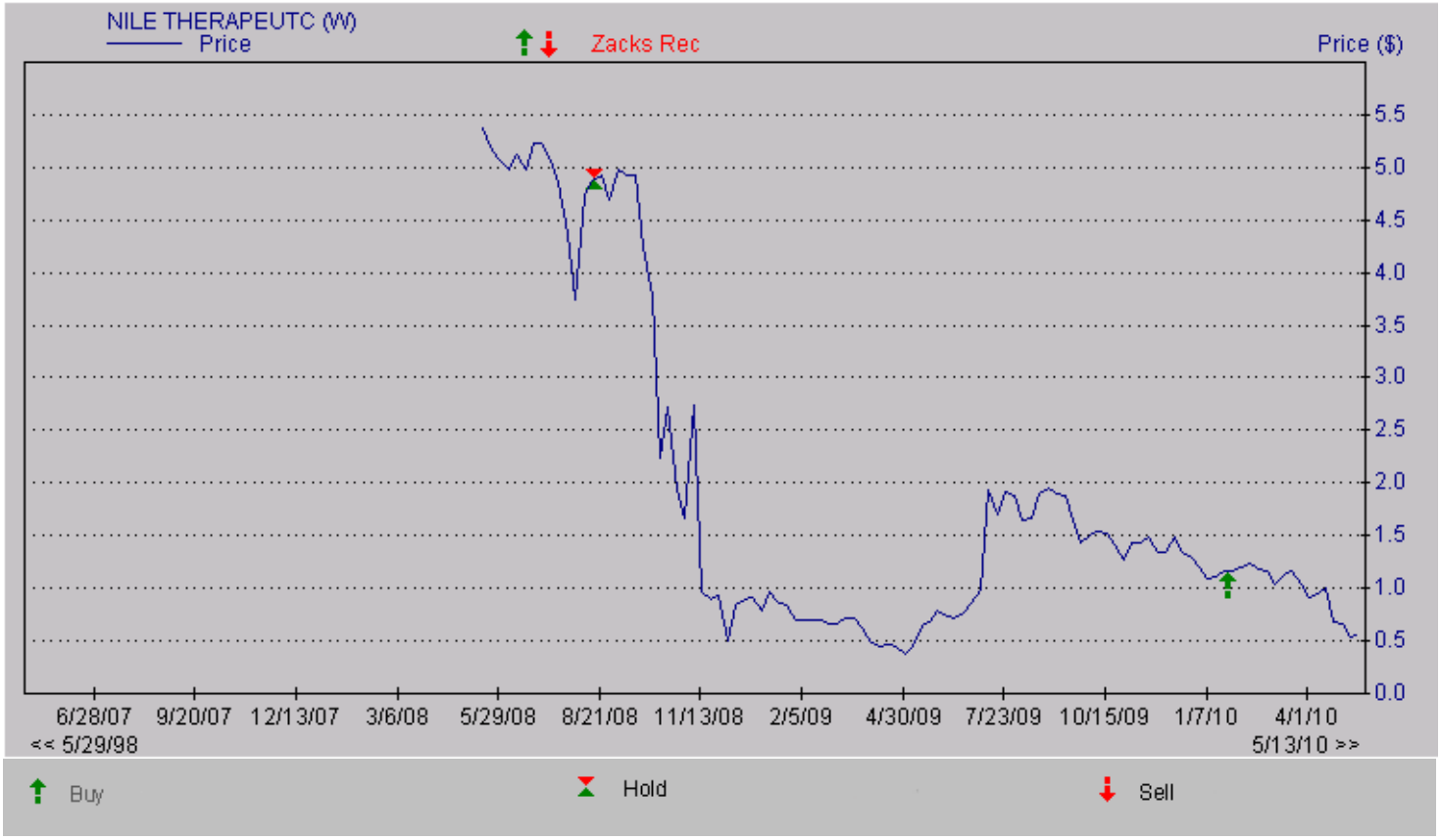
HISTORICAL ZACKS RECOMMENDATIONS



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