Zacks Small-Cap Research

September 16, 2015
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Tenax Therapeutics, Inc. (TENX – NasdaqCM)

TENX: Initiating Coverage of Tenax Therapeutics, Inc.; Targeting Critical Care with Levosimendan…

Current Recommendation	**Buy**
Prior Recommendation	N/A
Date of Last Change	09/16/2015
Current Price (09/16/15)	$3.65
Target Price	**$10.00**

INITIATION

We are initiating coverage of Tenax Therapeutics, Inc. (NasdaqCM: TENX) with a "Buy" rating and a price target of $10.00.

We believe the company's lead asset, levosimendan, is a relatively de-risked clinical development opportunity for the indication of low cardiac output syndrome (LCOS). To date, the drug has been used in over 1 million patients in more than 60 countries outside of North America. Levosimendan has FDA Fast Track status, and the ongoing Phase 3 LEVO-CTS trial has Special Protocol Assessment (SPA) designation. Trial data is expected in the latter part of 2016, and we see potential FDA approval occuring in 2017.

At the current price, we view Tenax shares as undervalued, and as providing significant long-term upside potential.

SUMMARY DATA

52-Week High	**$4.21**
52-Week Low	**$2.94**
One-Year Return (%)	**-10.98**
Beta	**0.07**
Average Daily Volume (sh)	**31,203**
Shares Outstanding (mil)	**28**
Market Capitalization ($mil)	**$103**
Short Interest Ratio (days)	**44.03**
Institutional Ownership (%)	**39**
Insider Ownership (%)	**16**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	**N/A**
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2013 Estimate	**N/A**
P/E using 2014 Estimate	**N/A**

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

ZACKS ESTIMATES

Revenue

(In millions of $)

	Q1 (July)	Q2 (Oct)	Q3 (Jan)	Q4 (Apr)	Year (Apr)
2014	$0.19 A	$0.06 A	$0.04 A	-$0.01 A	$0.29 A
2015	$0.00 A	$0.00 A	$0.00 A	$0.05 A	$0.05 A
2016	$0.00 A	$0.00 E	$0.00 E	$0.00 E	$0.00 E
2017					$25.25 E

Earnings per Share

(EPS is operating earnings before non-recurring items)

	Q1 (July)	Q2 (Oct)	Q3 (Jan)	Q4 (Apr)	Year (Apr)
2014	-$2.06 A	-$1.23 A	-$0.43 A	-$0.52 A	-$2.71 A
2015	-$0.08 A	-$0.14 A	-$0.14 A	-$0.14 A	-$0.50 A
2016	-$0.11 A	-$0.13 E	-$0.15 E	-$0.18 E	-$0.57 E
2017					$0.07 E

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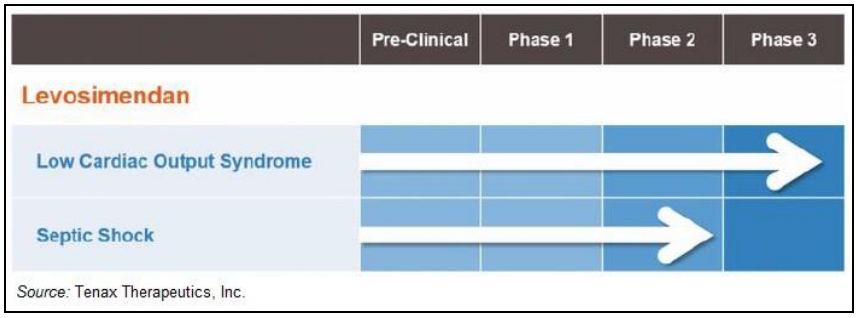
We are initiating coverage of Tenax Therapeutics, Inc. (NasdaqCM: TENX) with a "Buy" rating and a price target of $10.00. Tenax Therapeutics, Inc. is a development-stage specialty pharmaceutical company focused on the identification, development, and commercialization of products for critical care patients. The company is based in Morrisville, NC. Tenax's lead candidate, levosimendan, is currently being developed and evaluated in a Phase 3 trial for low cardiac output syndrome (LCOS) and a Phase 2 trial for septic shock (*below*). Outside of the U.S., the drug is currently approved and marketed as Simdax® (levosimendan i.v.) in more than 60 countries for patients with acute decompensated heart failure (ADHF). To date, according to the company, over 1 million patients worldwide have been prescribed the drug since its early 2000 launch.



As way of background, Tenax was first formed in 1967 as Rudmer, David & Associates, Inc., and later changed its name to Synthetic Blood International, Inc., and then to Oxygen Biotherapeutics, Inc. in June 2008. Six years later, in September 2014, the company was renamed Tenax Therapeutics, Inc. after acquiring the North American rights to levosimendan from Phyxius in November 2013. Previously, levosimendan was licensed by Phyxius from Finland-based Orion Corporation, which currently markets the drug under the brand name Simdax® in the EU. At this point, Tenax decided to suspend the development of Oxycyte®, a systemic perfluorocarbon (PFC) product for the treatment of traumatic brain injury, sickle cell pain crisis, decompression sickness, stroke, heart attack, and wound treatment, which had previously been the primary focus of Oxygen Biotherapeutics, and shifted all focus to levosimendan for the reduction of mortality and morbidity in cardiac surgery patients at risk of developing LCOS and for the indication of septic shock.

The U.S. Food and Drug Administration (FDA) has granted Fast Track status for levosimendan and has also agreed to Tenax's Phase 3 clinical trial protocol under a Special Protocol Assessment (SPA) in 2012. The goal of the Phase 3 LEVO-CTS (*Levosimendan in Patients With Left Ventricular Systolic Dysfunction Undergoing Cardiac Surgery On Cardiopulmonary Bypass*) clinical trial is to evaluate if levosimendan administered before and during surgery will reduce the incidence of morbidity and mortality in cardiac surgery patients at risk of LCOS. As per management, the FDA has provided guidance that a single successful trial will be sufficient to support approval of levosimendan for the indication mentioned above. We believe that LEVO-CTS will most likely be completed during the second half of 2016, and look forward to reviewing the Phase 3 data once available. If all goes well, we think approval could occur at some point during the first half of calendar 2017.

Additionally, Tenax is collaborating with the Imperial College of London for the accelerated enrollment and completion of the ongoing Phase 2b LeoPARDS Trial *(Levosimendan for the Prevention of Acute oRgan Dysfunction in Sepsis*). The LeoPARDS trial aims to evaluate if levosimendan reduces the incidence and severity of acute organ dysfunction in adult patients who have septic shock, as well as assess its safety profile.

In our opinion, the Tenax development portfolio includes a novel product candidate that has the potential to address various critical care conditions with high unmet medical need. We view levosimendan as a relatively de-risked clinical development opportunity for the indication of LCOS due to the prior usage of the drug in over 1 million patients in over 60 countries around the world. We also view septic shock as an area of unmet clinical need, as the condition is often associated with high mortality, morbidity and critical care costs.

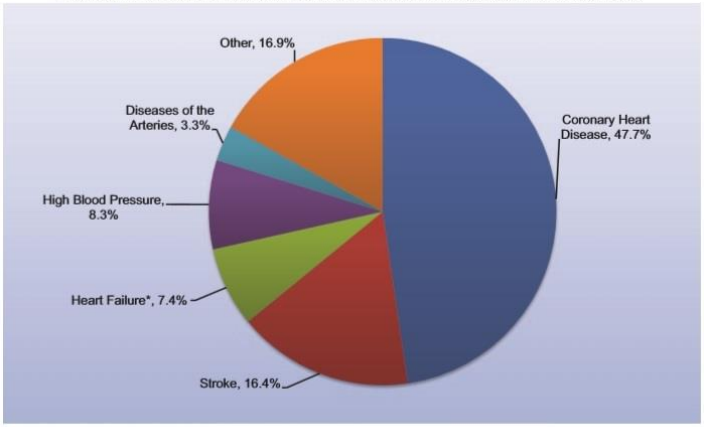
INVESTMENT THESIS

Cardiovascular Disease: #1 Cause of Death Worldwide

Cardiovascular disease (CVD) refers to a category of diseases that involve the circulatory system including the heart and blood vessels. The World Health Organization (WHO) reported that more than 17.5 million people died from cardiovascular diseases in 2012, which represents 31% of all deaths worldwide. As a reference point, 7.5 million out of the 17.5 million CVD deaths were due to coronary heart disease, and 6.7 million were due to stroke. This makes CVD the number one cause of death globally. The WHO estimates that by 2030, more than 23 million people will die annually from cardiovascular diseases.

It is important to highlight that in every year since 1900 (except 1918), CVD was responsible for more deaths than any other cause of death in the United States (Ford *et al*., 2007 and NCHS - NHLBI public use data file, 2011). According to the U.S. CDC, approximately 610,000 individuals die of heart disease in the U.S. every year, which is approximately 1 in every 4 deaths. CVD is the leading cause of death in both men and women in the U.S., with coronary heart disease being the most common type of CVD resulting in over 370,000 deaths annually (*right*). According to the most current statistical update from the American Heart Association, more than 85 million American adults have one or more types of cardiovascular disease, with approximately 43.7 million of these being ≥60 years old (Mozaffarian *et al*., 2015).

Percentage breakdown of deaths attributable to cardiovascular disease (United States: 2011)



Sources: National Heart, Lung, and Blood Institute from National Center for Health Statistics; Heart Disease and Stroke Statistics—2015 Update: A Report from the American Heart Association. *Circulation.* 2015;131:e29–e322.

The Economic Burden of Cardiovascular Disease

CVD and stroke accounted for 15% of total health expenditures in 2011 in the United States, which is more than any other major diagnostic group (MEPS, 2011). In the U.S., the total direct and indirect costs of CVD and stroke for 2011 were estimated to be about $320.1 billion per year. This value includes $195.6 billion of direct expenses associated with the cost of physicians and other health care providers, hospital services, medication, and home health care as well as $124.5 billion of indirect expenses of lost future productivity due to premature CVD and stroke mortality in 2011 (*right*). By way of comparison, CVD and stroke direct costs of $195.6 billion are far higher than that of the National Cancer Institute estimates for cancer in 2011 of $88.7 billion in direct costs.

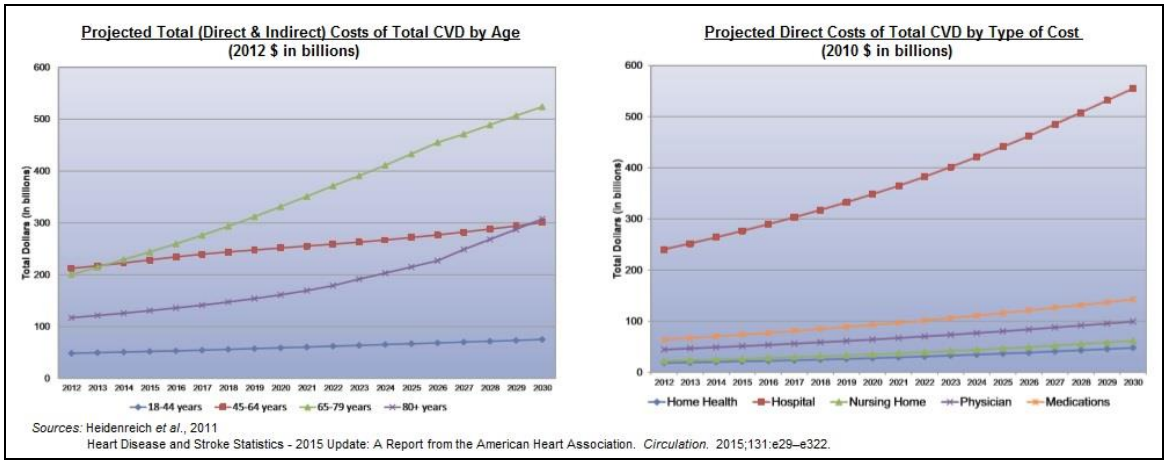
Estimated Direct and Indirect Costs (in Billions of Dollars) of CVD and Stroke: United States, 2011

	Heart Disease*	Stroke	Hypertensive Disease†	Other Circulatory Conditions	Total CVD
Direct costs‡					
Hospital inpatient stays	70.5	7.6	4.9	8.7	91.7
Hospital emergency department visits	4.8	1.2	1.5	0.6	8.1
Hospital outpatient or office-based provider visits	23.1	2.0	13.5	5.9	44.5
Home health care	6.6	5.1	3.9	2.3	17.9
Prescribed medicines	11.3	1.7	19.0	1.5	33.5
Total expenditures	116.3	17.5	42.8	19.0	195.6
Indirect costs§					
Lost productivity/mortality‖	99.3	16.0	3.6	5.6	124.5
Grand totals	215.6	33.6	46.4	24.6	320.1

Numbers do not add to total because of rounding.
CVD indicates cardiovascular disease.
*This category includes coronary heart disease, heart failure, part of hypertensive disease, cardiac dysrhythmias, rheumatic heart disease, cardiomyopathy, pulmonary heart disease, and other or ill-defined heart diseases.
†Costs attributable to hypertensive disease are limited to hypertension without heart disease.

Sources: Agency for Healthcare Research and Quality; National Center for Health Statistics; Wendy Max - Institute for Health and Aging (UCSF). Heart Disease and Stroke Statistics - 2015 Update: A Report from the American Heart Association. *Circulation.* 2015;131:e29–e322. Estimates prepared by Michael Mussolino, National Heart, Lung, and Blood Institute

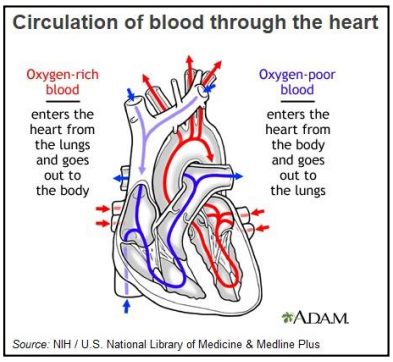
It has been estimated that the total direct medical costs of CVD will increase from $396 million in 2012 to roughly $918 billion by 2030 (*bottom left*) in the United States. Of these direct costs, 60.5% is due to hospital related expenses, 15.6% to medications, 10.8% to physicians, 6.8 % to nursing home care, 5.3% to home health care, and 1.1% to other costs (*bottom right*). Indirect costs for all CVDs are estimated to increase from $183 billion in 2012 to $290 billion in 2030, which equates to an increase of 58%. It is projected that by 2030, 44% of Americans will have some form of cardiovascular disease (Heidenreich *et al*., 2011). Additionally, the estimated cost of CVD worldwide in 2010 was $863 billion, and this cost is estimated to increase to $1044 billion by 2030 (Bloom *et al*., 2011).



Sources: Heidenreich *et al.*, 2011
Heart Disease and Stroke Statistics - 2015 Update: A Report from the American Heart Association. *Circulation.* 2015;131:e29–e322.

A Brief Overview of Cardiac Function

The heart is a complicated and powerful organ that is responsible for pumping blood throughout the body; delivering oxygen and nutrients to tissues and other organs while eliminating carbon dioxide and waste products. As the heart beats, oxygen-rich blood is circulated from the heart to areas such as the brain, tissues, and extremities, while oxygen-poor blood is transported from the body to the lungs in order to become oxygenated (NHLBI, 2011) (*right*). Approximately five to six liters, or approximately 1.5 gallons, of blood are pumped by the heart every minute to various parts of the body in an average healthy adult (Healthwise, Rakesh Pai, M.D., Stephen Fort, M.D., 2014). This is equivalent to over 2,000 gallons of blood being pumped by the heart each day.

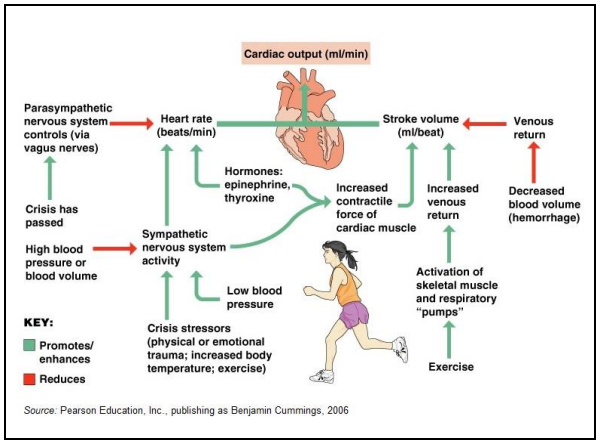


Source: NIH / U.S. National Library of Medicine & Medline Plus

What is Cardiac Output?

Cardiac output refers to the amount of blood that the heart pumps to the systemic circulation in one minute, and is typically expressed in milliliters or liters per minute (mL/min or L/min). Cardiac output is one way of measuring how efficiently the heart is pumping blood. Factors that can contribute to cardiac output regulation can be seen in the image below. Cardiac output is dependent on *heart rate*, *contractility*, *preload* (the degree of myocardial distension prior to shortening), and *afterload* (the force against which the ventricles must act in order to eject blood) (Vincent, 2008). If any of these interrelated components are affected by certain situations or disease processes, a low cardiac output state can arise (Massé *et al.*, 2005). Cardiac output is often calculated using the formula below:

CARDIAC OUTPUT = *heart rate* [heart beats/min] *x stroke volume* [volume of blood that is pumped out of the heart with each beat]



Source: Pearson Education, Inc., publishing as Benjamin Cummings, 2006

Cardiac output represents the total blood flow in the body. If stressful situations arise, cardiac output is altered so that the needs for organs and tissues are satisfied (Massé *et al.*, 2005). For the heart to work optimally, there are many components that need to work together in order to pump blood throughout the body. Heart disease, in

addition to other diseases and conditions, can compromise the normal pumping capabilities and electrical system of the heart, and thus makes it difficult for the heart to pump blood properly (NHLBI, 2011). It is generally accepted that on average, a healthy adult heart will pump about 5 liters of blood per minute, and thus have a cardiac output of 5 L/min. It is important to maintain adequate cardiac output in order to keep blood pressure at an optimal level in addition to being able to supply oxygen-rich blood to the brain and other vital organs (Healthwise, Rakesh Pai, M.D., Stephen Fort, M.D., 2014). If cardiac output is too low, then the body is not getting enough blood, which can lead to life threatening situations if not addressed immediately.

A Dangerous Situation: Low Cardiac Output Syndrome

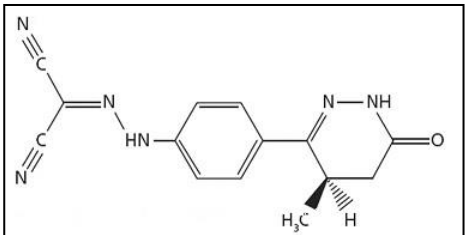
When cardiac output is not at an optimal level, a situation known as low cardiac output syndrome, or LCOS, can arise. LCOS refers to the state when there is reduced cardiac output due to transitory dysfunction of the heart. It is associated with certain disease states as well as shock, and can occur in patients that have undergone cardiac surgery. Early diagnosis of LCOS is important in order to prevent complications, including death, which may result due to inadequate systemic perfusion (Massé *et al.*, 2005). LCOS is often considered a form of acute heart failure, or AHF (Álvarez, 2008). Immediate management and treatment of LCOS is necessary in order to maintain proper nutrient delivery and oxygen supply to the periphery (Massé *et al.*, 2005). LCOS is one of the most serious outcomes that can arise in cardiac surgery patients. It is often associated with high morbidity and mortality rates as well as increased costs and resources related to prolonged hospital and critical care stays (Kirklin *et al.*, 1993; Rao *et al*., 1996; Levin *et al*., 2008).

Although we found that the reported incidence rates appear to vary across published data and were as high as 20% in certain studies, based on our research we believe that LCOS can occur in 5 to 10% of patients undergoing cardiac surgery (Rao *et al*., 1996; Álvarez, 2008). In addition, it can be associated with a 10 to 15 fold higher mortality or severe sequelae due to poor organ perfusion such as kidney failure and/or end stage renal disease (Cohn, 2007; Rao *et al*., 1996; Bojar, 2005; Maganti *et al*., 2005; Maganti *et al*., 2010). Currently, there are no approved therapeutics on the market that can prevent, reduce, or treat the occurrence of LCOS. There are certain risk factors for cardiac surgery patients that increase the chance for developing LCOS, including left ventricular dysfunction, prior coronary artery bypass graft (CABG) surgery, diabetes, being over the age of 70, and being female.

It is generally accepted that LCOS refers to the clinical condition when an individual is unable to maintain a cardiac index of > 2.2 L/min/m^2 without relative associated hypovolemia (Pérez *et al*., 2012). Management usually involves treating the cause, alleviating symptoms, and stabilizing hemodynamics, with the goal to re-establish proper perfusion and oxygen to organs (Mathieu *et al*., 2011). Stabilizing an LCOS patient typically requires a complex treatment plan including the use of some combination of inotropic beta-adrenergic receptor agonists and/or phosphodiesterase III inhibitors, diuretics, vasodilatory agents, and/or mechanical assisted devices (such as intra-aortic balloon pump or a left ventricular assist device) (Levin *et al*., 2008; Mathieu *et al*., 2011). Traditional inotropes are drugs that either increase (positive inotrope) or decrease (negative inotrope) the strength of the muscular contraction of the heart, and have been used to manage cardiac hemodynamics in the short-term peri-operative setting, but can be associated with increased risk of morbidity and death (Maharaj *et al*., 2011; Mathieu *et al*., 2011). This leads us to believe that there is a major opportunity to improve hemodynamics and survival outcomes for patients with LCOS via novel treatment options and approaches.

The Levosimendan Story

As mentioned above, there are currently no pharmacologic agents that are approved for the management, prevention and/or treatment of post-cardiac surgery LCOS. To address the issues outlined above surrounding LCOS, Tenax hopes to offer a solution with levosimendan, and believes that if administered pre- and peri-operatively, the incidence of LCOS and the associated morbidity and mortality could be decreased.



Source: Nieminen *et al.*, 2013

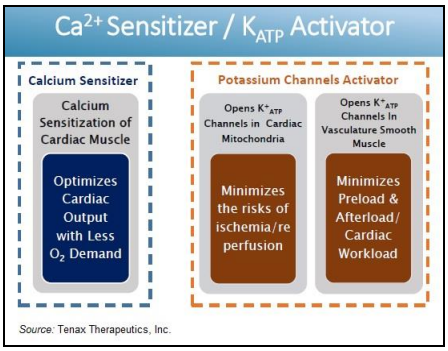
Tenax's lead asset, levosimendan, is a novel, first-in-class calcium sensitizer/K-ATP activator for intravenous (IV) use in hospitalized patients, originally developed by Orion Corporation in Finland, and first launched in the EU in 2000 for the short-term treatment of acute decompensated heart failure (ADHF) where conventional therapy is not sufficient, and in cases where inotropic support is considered appropriate. Outside of the U.S., the drug is currently approved and marketed as Simdax® (levosimendan i.v.) in more than 60 countries around the globe for patients with ADHF. According to the company, over 1 million patients worldwide have been prescribed the drug, with significant off-label use of the drug in the EU. The patent for the Simdax® molecule in Europe expires in September

2015, and the product generated revenues in 2014 of approximately €47 million Euros (approximately $53 million USD at the exchange rate as of August 20, 2015).

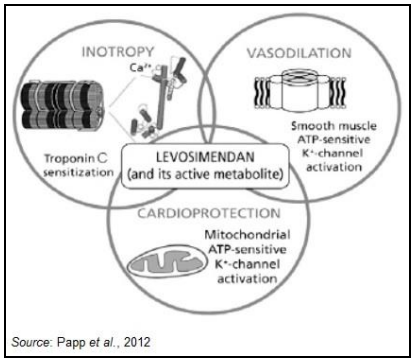
Phyxius was granted the North American rights to levosimendan in 2011, and Tenax went on to acquire Phyxius in 2013. Tenax currently holds a license from Orion to develop and commercialize pharmaceutical products that contain levosimendan 2.5 mg/ml concentrate for solution for infusion / 5 ml vial in North America, under the brand name Simdax®. Tenax initiated a Phase 3 trial, which we will address in further detail below, in the third quarter of calendar year 2014. Under the terms of the agreement, Tenax must pay Orion a $2 million milestone payment upon FDA approval, $1 million upon Canadian approval, up to $13 million in potential commercial milestones payments based on achieving certain cumulative sales amounts, as well as tiered royalties based on net sales.

Tenax is currently developing the drug in the U.S. and Canada for the reduction of morbidity and mortality in cardiac surgery patients at risk for developing low cardiac output syndrome (LCOS). Levosimendan has been granted Fast Track status by the U.S. Food and Drug Administration (FDA), which has approved Tenax's Phase 3 LEVO-CTS clinical trial protocol under a Special Protocol Assessment (SPA). Tenax is also pursuing an additional indication for levosimendan as it pertains to septic shock.

Triple Mechanism of Action of Levosimendan

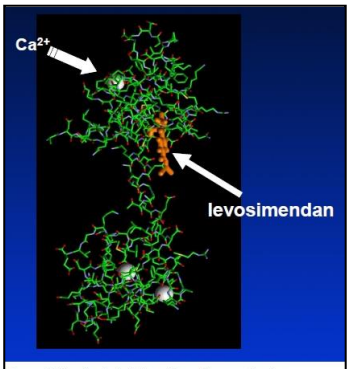


Levosimendan is a calcium sensitizer/K-ATP activator, and the therapeutic effects are achieved via a triple mechanism of action (MOA) through increased force of muscular contractions (positive inotropic effect), vasodilation, and cardioprotection (*above*). The triple MOA of action helps differentiate levosimendan from other inodilators such as milrinone, dobutamine, and dopamine. It has been proposed that this triple MOA also helps to preserve heart function during cardiac surgery, and studies have demonstrated that levosimendan protects the heart and improves tissue perfusion while minimizing tissue damage during cardiac surgery. In the body, levosimendan is completely metabolized and about 5% of the dose infused is first converted to OR-1855 in the large intestine, and then subsequently acetylated to the active metabolite OR-1896 in the liver. OR-1896 is 40% bound to plasma proteins and has an elimination half-life of 75-80 hours vs. levosimendan, which is 98% bound to plasma proteins and only has a half-life of 1 hour. OR-1896 reaches a peak plasma concentration approximately 2 days after the termination of infusion, and it exhibits similar hemodynamic effects to levosimendan through calcium sensitization and vasodilation. Because of the extended half-life of OR-1896, these effects can last up to 7 to 9 days after infusion has been terminated (Nieminen *et al.*, 2009).



➢ **Levosimendan as a Calcium Sensitizer (*Contractility*)**

Levosimendan is a calcium sensitizer and increases the sensitivity of the heart to calcium. By doing this, it is able to increase cardiac contractility by targeting contractile proteins in cardiomyocytes, or heart muscle cells, without increasing intracellular calcium levels and without substantial increases in oxygen demand. Levosimendan has a positive inotropic effect by selectively binding to cardiac troponin C that is saturated with calcium (*see figure on the right*). In other words, levosimendan can improve contraction of the heart with low energy costs, and since it does not disrupt calcium levels, unlike other ionotropic agents, it does not cause cardiomyocyte dysfunction. Increased calcium levels can cause arrhythmias (Kasikcioglu *et al*., 2006). On the other hand, inotropes such as dobutamine (stimulate β1 receptors) and milrinone (inhibits phosphodiesterase) also increase cardiac output but do so via increased heart rate and myocardial oxygen demand.



Source: Pollesello *et al*., 1994 and Tenax Therapeutics, Inc.

➢ **Levosimendan as a Potassium Channel Activator (*Vasodilation*)**

Levosimendan is a potassium channel activator and opens adenosine triphosphate (ATP)-sensitive potassium channels in vascular smooth muscle. This results in smooth muscle relaxation or a vasodilatory effect on all vascular beds (Nieminen *et al.*, 2013), including venous, arterial, and coronary vasodilation (Figgitt *et al*., 2001).

➢ **Levosimendan as a Potassium Channel Activator (*Cardioprotection*)**

Levosimendan is a potassium channel activator and also opens mitochondrial adenosine triphosphate (ATP)-sensitive potassium channels in cardiomyocytes, resulting in a cardioprotective effect (Pollesello *et al.*, 2007). In addition, the vasodilating effects of the K-ATP mechanism produces a reduction in both preload and afterload (Harkin *et al.*, 1995), and an increase in coronary blood flow (Kaheinen *et al*., 2001) with overall improved myocardial tissue perfusion.

Many researchers believe that levosimendan's triple mechanism of action may provide cardiac surgery patients with several benefits, and the rationale for use in the setting is summarized below:

Levosimendan Mechanism	Physiologic Effect	Potential Benefits for Cardiac Surgery Patients
Calcium Sensitizer	Oxygen Sparing Increase in Cardiac Output (1,2)	Oxygen Efficient Increase in Post-Op Cardiac Reserve/Output
K-ATP Channel Activator-Mitochondria	Protects Cardiac Cells During Ischemia (3,4)	Reduced Peri-Op Myocardial Infarction
K-ATP Channel Activator-Vascular Smooth Muscles Cells	Improved microcirculatory blood flow (5,6)	Improved Post Op Organ Perfusion

Improved Outcomes

Source: Tenax Therapeutics, Inc.

1. De Hert et al., 2007; 2. Eriksson et al., 2009; 3. Zangrillo et al., 2009; 4. Tritapepe et al., 2009; 5. Bragadottir et al., 2013; 6. Baysal et al, 2014

Scientific Evidence that Supports Levosimendan in Cardiac Surgery

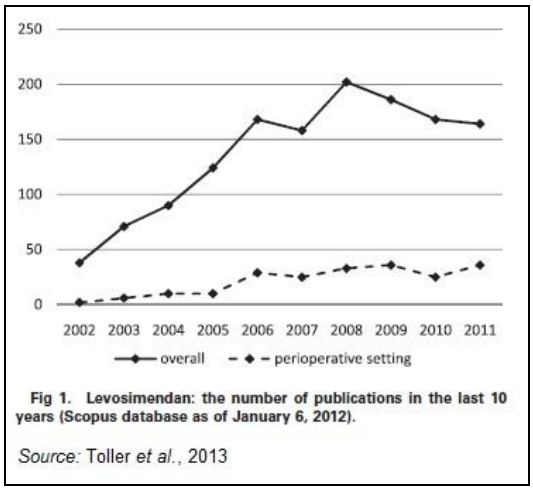
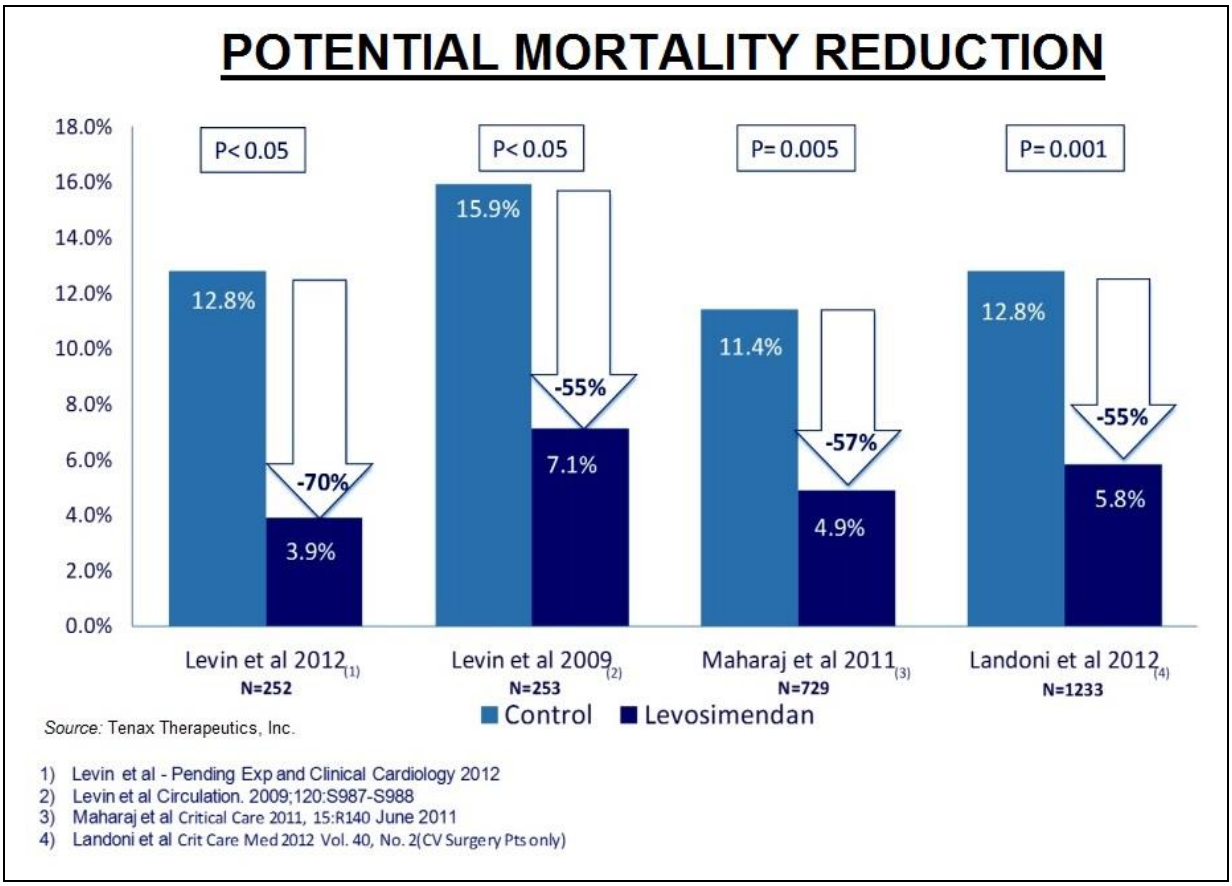


Fig 1. Levosimendan: the number of publications in the last 10 years (Scopus database as of January 6, 2012).

Source: Toller *et al.*, 2013

There is substantial scientific evidence that supports the use of levosimendan in cardiovascular surgery, with over 35 published clinical trials, meta-analyses, and articles appearing in peer-reviewed journals to date. Researchers have stated that levosimendan is one of the most studied inotropic agents to date (*above*) (Toller *et al*., 2013), and we believe that interest surrounding the drug continues to rise. There is evidence of mortality reduction in some clinical trials of more than 50% (*below*), with positive trends in improvement of morbidity outcomes, hemodynamic and cardioprotective effects, renal function, as well as reduced hospital / ICU stays and costs. We believe that existing data demonstrates the potential value in cardiac surgery patients.



We would like to highlight a recent meta-analysis (Lim *et al.*, 2015) that examined levosimendan's role in cardiac surgery patients. The meta-analysis pooled data from 14 prior clinical trials, and showed that levosimendan decreased early mortality in patients with reduced ejection fraction (5.5% for levosimendan vs. 9.1% for the control

group), reduced postoperative acute renal failure, resulted in a shorter stay in the intensive care unit (ICU), and resulted in a lower incidence of LCOS for the levosimendan group in trials.

A recent expert EU opinion paper (Toller *et al.*, 2015) of 27 panel members from 18 countries reiterated the positive trends associate with levosimendan usage observed in cardiac surgery patients to date, including improvement of general and pulmonary hemodynamics, optimization of renal and hepatic function, and the reduction of need for inotropic agents and mechanical circulatory support. The paper offers a systemic review of the literature on past and ongoing studies on levosimendan, including Tenax's Phase 3 LEVO-CTS study (*below*). The expert paper supported the dose protocol that is currently being used by Tenax in LEVO-CTS. The paper agreed that studies have shown the effectiveness of the drug, and that levosimendan treatment can be used as a "safety net" in surgical settings. By doing so, levosimendan can help to reduce postoperative complications and hospital / ICU stays for patients due to its unique inotropic and cardioprotective properties. However, with levosimendan treatment, vasodilation is known to occur, which then warrants combination therapy of levosimendan with norepinephrine or vasopressin, and if additional inotropic support is required in a levosimendan-treated patient, dobutamine should used.

Table 3: Ongoing clinical trials on the use of levosimendan in cardiac surgery.

Study indicators: title, acronym, NCT number and main investigator (when available)	Patient population	Patient number	Levosimendan dose and time	Comparator	Endpoints
LICORN (P110138) B. Cholley	Patients with LVEF ≤40% undergoing CABG with or without valve replacement under CPB	340	0.1 µg/kg/min infusion for 24 h, started at the time of anaesthesia induction, without bolus application.	Placebo	Composite primary endpoint including use of inotropic agents beyond 24 h after end of study drug infusion, or need for postoperative mechanical assist devices (IABP or others), or impossibility to wean patients from them if they were already in use preoperatively, or the need for renal replacement therapy. Secondary endpoints comprise mortality at days 28 and 180, each item of the primary endpoint separately, and length of intensive care unit and hospital stays.
Intracoronary administration of levosimendan in cardiac surgery patients, (NCT01500785) K. Järvelä	Patients undergoing aortic valve and CABG surgery	50	Intracoronary 12 µg/kg infusion, initiated at the induction of cardioplegia	Placebo	Primary endpoint of change in cardiac output 15 min after separation from CPB, compared to baseline. Secondary endpoints include change in LVEF between baseline and 5 min after sternal closure, and cTnT/CK-MB levels of first postoperative morning
LEVO-CTS (NCT02025621) R. H. Mehta	Patients undergoing CABG (LVEF ≤25%) and/or mitral valve surgery (LVEF ≤35%)	760	0.2 µg/kg/min infusion for 1 h followed by 0.1 µg/kg/min infusion for 23 h, started before surgery.	Placebo	Two co-primary endpoints: • All-cause death at 30 days or use of mechanical assist device to day 5 • All-cause death at 30 days, or perioperative non-fatal myocardial infarction to day 5, or need for renal dialysis to day 30, or use of mechanical assist device to day 5 Secondary endpoints: • Length of intensive care unit/ coronary care unit stay • Incidence of post-operative low cardiac output syndrome • Postoperative use of secondary inotrope
Aristotle University of Thessaloniki, Greece K. Anastasiadis	Patients with left ventricular dysfunction (LVEF ≤40%) scheduled for CABG	32	0.1 µg/kg/min infusion for 24 h before surgery	Placebo	Primary endpoint of assessment of left ventricular function by transthoracic echocardiography on 7th postoperative day. Secondary endpoints of cardiac index, tissue perfusion, and PCWP.
HSR-LEVO (NCT00994825) G. Landoni	High risk patients undergoing cardiac surgery with perioperative myocardial dysfunction	1000	24-48 h infusion (varying doses)	Placebo	Primary endpoint of 30-day mortality

Source: Toller *et al.*, 2015

A Bayesian network meta-analysis recently compared the effectiveness of various inodilators such as dobutamine, enoximone, levosimendan, and milrinone on the survival of adult cardiac surgery patients (Greco *et al.*, 2015). The meta-analysis pooled data from 46 trials from 1995 to 2014, and randomized 2647 patients. The analysis concluded that levosimendan appeared to be the most efficacious inodilator to improve survival in cardiac surgery, and that only the use of levosimendan was associated with a decrease in mortality when compared with placebo (posterior mean of OR=0.48, 95% CrI 0.28 to 0.80), however the sensitivity analyses performed did not produce different interpretative results (*below*).

Table 4 Posterior distribution of the probability to be the best and the worst for each inodilators drug, derived by Bayesian hierarchical model with Markov Chain Monte Carlo algorithm

Drugs	Overall Bayesian network meta-analysis		Combining enoximone and milrinone groups	
	Probability to be the best	Probability to be the worst	Probability to be the best	Probability to be the worst
Levosimendan	0.5146	0.0001	0.9088	0.0002
Enoximone	0.4424	0.5421	0.0674	0.2874
Milrinone	0.0302	0.1370		
Dobutamine	0.0114	0.2605	0.0028	0.1274
Placebo	0.0014	0.0603	0.0028	0.1274

Source: Greco *et al.*, 2015

Orion/Abbott's Clinical Development Program for Simdax®

Orion and Abbott Laboratories entered into a partnership under a marketing agreement for Simdax® in early 1998. Abbott gained worldwide rights to further develop and commercialize Simdax® in April 2004, assuming clinical and financial responsibility for R&D programs, while Orion retained rights to market the product in Finland, Sweden, Norway, Iceland and Denmark, with co-promotion rights in Hungary, Russia and Ukraine. Orion retained the patent rights to levosimendan and all rights to veterinary applications and non-injectable formulations such as orally administered levosimendan. In April 2007, it was announced that Abbott discontinued levosimendan development, and that additional Phase 3 studies would not be completed by the company. Orion reacquired all rights for levosimendan in May 2009, except for certain Latin American countries where Abbott markets the product.

Prior to gaining approval outside of the U.S., the clinical development program for Simdax® (levosimendan i.v.) involved close to 3,500 patients, many with worsening acute decompensated heart failure (ADHF). The trials are summarized in the table below, and we will proceed to review some of the major studies in the program for background (Simdax®, 2010).

Study	N (Total [Levo])	Dose and duration	Comparator	Diagnosis (NYHA class)	Primary endpoint
Dose-ranging	151 [95]	0.05–0.6 mcg/kg/min; 24 h	Placebo or dobutamine	CHF [III]	Haemodynamics
Escalation & withdrawal	146 [98]	0.1–0.4 mcg/kg/min; 24 or 48 h	Placebo	CHF [III]	Haemodynamics
LIDO	203 [103]	0.1–0.2 mcg/kg/min; 24 h	Dobutamine	CHF [III–IV]	Haemodynamics
RUSSLAN	504 [402]	0.1–0.2 mcg/kg/min; 6 h	Placebo	Post-AMI [IV]	Safety
REVIVE I	100 [51]	0.1–0.2 mcg/kg/min; 24 h	Placebo	CHF [IV]	Clinical composite
REVIVE II	600 [299]	0.1–0.2 mcg/kg/min; 24 h	Placebo	CHF [IV]	Clinical composite
SURVIVE	1327 [664]	0.1–0.2 mcg/kg/min; 24 h	Dobutamine	CHF [IV]	Mortality

AMI = acute myocardial infarction; CHF = chronic heart failure; Levo = levosimendan; NYHA = New York Heart Association

Source: Kivikko, M. & Tenax Therapeutics, Inc.

- **LIDO** (Follath *et al*., 2002): The LIDO (*Levosimendan Infusion versus Dobutamine*) study was a double-blind, multi-center, randomized trial of 203 patients with low output heart failure requiring right heart catheterization as well as intravenous (i.v.) inotropic drug therapy. The goal of the study was to evaluate the safety and efficacy of i.v. levosimendan vs. dobutamine, and this trial was the primary driver for the initial approval of the drug in the EU. Patients either received levosimendan as an initial i.v. bolus of 24 µg/kg over 10 min, followed by a 24 hour i.v. infusion of levosimendan at doses from 0.1-0.2 µg/kg/min or 5-10 µg/kg/min of dobutamine for 24 hours. The primary endpoint was an increase in cardiac output by ≥ 30%, and a decrease of pulmonary capillary wedge pressure (PCWP) by ≥ 25% at 24 hours. It was found that in patients with severe, low-output heart failure, levosimendan was better at improving hemodynamic performance than dobutamine with lower mortality in the levosimendan group for up to 180 days. A retrospective analysis of LIDO showed that there was no observable adverse effect on survival for up to 6 months.

- **RUSSLAN** (Moiseyev *et al*., 2002): The RUSSLAN (*Randomized Study on Safety and Effectiveness of Levosimendan in Patients with Left Ventricular Failure after an Acute Myocardial Infarct*) study was a randomized, placebo-controlled, double-blind, parallel-group trial of 504 patients in Europe that were enrolled within days of following an acute myocardial infarction, and compared levosimendan, infused for 6 hours at 4 different doses, with placebo. Patients that were randomized to receive levosimendan were treated with a bolus dose of 6-24 µg/kg over 10 min, followed by a 6 hour intravenous infusion at rates ranging from 0.1 to 0.4 µg/kg/min. The primary endpoint was hypotension or myocardial ischemia of clinical significance determined by an independent safety committee, and secondary endpoints included risk of death and worsening heart failure, symptoms of heart failure and all-cause mortality. It was found that levosimendan at doses 0.1-0.2 µg/kg/min did not increase the incidence of hypotension or ischemia, and reduced the risk of death and worsening heart failure in patients over 24 hours (4.0% vs. 8.8% in placebo group; p=0.044). Mortality was 19.6% with placebo vs. 11.7% with levosimendan at 14 days (p=0.031), but after 180 days the differences were no more statistically significant. A retrospective analysis of RUSSLAN showed that there was no observable adverse effect on survival for up to 6 months.

- **REVIVE I & REVIVE II** (Packer *et al.*, 2013): The REVIVE (*Randomized Multi-center Evaluation of Intravenous Levosimendan Efficacy*) clinical program consisting of REVIVE I and REVIVE II was designed to evaluate the safety and efficacy of i.v. levosimendan plus standard of care therapy vs. placebo plus standard of care therapy

for 24 hours in patients with acute decompensated heart failure (ADHF). Two sequential trials were performed. REVIVE I was a double-blind, placebo-controlled pilot study of 100 patients with ADHF who received a 24 hour infusion of i.v. levosimendan, and results showed a beneficial response as measured by the composite endpoint over placebo plus standard of care therapy.

REVIVE II was a double-blind, placebo-control pilot study of an additional 600 patients with ADHF who received a 10 minute loading dose of 6-12 µg/kg of levosimendan followed by a protocol-specified steeped titration of levosimendan of 0.05-0.2 µg/kg/min for up to 24 hours. The primary endpoint was a composite that evaluated changes in clinical status during the first 5 days after randomization, and showed that more levosimendan patients vs. placebo patients (58 vs. 44) were categorized as improved at all 3 pre-specified time points (6 hours, 24 hours, 5 days), with a smaller proportion (58 levosimendan vs. 82 placebo) experiencing clinical worsening (p=0.015 for the difference between the groups). B-type natriuretic peptide levels were reduced for 5 days vs. placebo and standard of care therapy with reduced length of stay (p=.009). However, it is important to know that levosimendan was associated with more frequent occurrences of hypotension and cardiac arrhythmias during the infusion period, in addition to having a higher death rate (49 of 350 for levosimendan vs. 40 of 350 for placebo at 90 days, p = 0.29). Although, i.v. levosimendan provided fast, symptomatic relief for patients with ADHF, as dosed in the program, the drug was associated with an increased risk of adverse cardiovascular events.

- **SURVIVE** (Mebazaa *et al*., 2009): The SURVIVE (*Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support*) study was a randomized, double-blind, double-dummy, parallel-group, multi-center study of 1327 patients with ADHF, and compared the effects of levosimendan vs. dobutamine on 180-day mortality. Patients that were randomized to receive standard of care + levosimendan were treated with a bolus of 12 µg/kg over 10 min, followed by a 24 hour intravenous infusion of 0.1-0.2 µg/kg/min, while the average dose of dobutamine was 6 µg/kg/min. Patients were admitted to the ICU but were not monitored invasively. Patients were also allowed to receive i.v. diuretics and vasodilators simultaneously. Approximately 90% of patients were enrolled due to having dyspnea (shortness of breath) at rest. Results did not show a statistically significant difference between levosimendan and dobutamine in 180-day all-cause mortality (p=0.401). Patients with low baseline blood pressure experienced higher mortality rates than those with higher baseline blood pressure.

We believe that there are several reasons as to why the SURVIVE and REVIVE II trials run by Abbott Laboratories from 2003-2005 were unsuccessful. With initial results of the large clinical program (LIDO & RUSSLAN) being positive, the contradictory results from SURVIVE and REVIVE II lead us to believe that the study designs were flawed. First off, we believe that pre-screening of patients for proper patient selection is of utmost important. In the later trials, Abbott included patients that were hypotensive, and post hoc analysis showed that low blood pressure with SBP < 100 mm Hg or DBP < 60 mm Hg at baseline was associated with increased mortality risk. Secondly, patients in SURVIVE and REVIVE II were not invasively monitored using a pulmonary artery catheter during levosimendan infusions. Doing so would have provided critical data and direct measurements regarding important hemodynamic parameters such as pulmonary capillary wedge pressure and cardiac index. In the LIDO trial, for example, all patients were hemodynamically monitored, and had initial capillary wedge pressures ≥ 15 mm Hg, a cardiac index < 2.5 L/kg/m^2, and co-administration of diuretics or vasodilators was not allowed. With these limitations in place, patients that may have had signs of myocardial ischemia or arrhythmias were excluded from the trial from the beginning. On the other hand, in both REVIVE II and SURVIVE, simultaneous treatment with the above mentioned drugs, sometimes at high doses, was allowed without proper monitoring. Research suggests that drug-induced hypovolemia and hypokalemia due to increased administration of diuretics could not be excluded and are likely to have been present in many of the cases. We also believe that there were dosing-related issues, as patients in SURVIVE received greater than necessary levels of levosimendan. Since levosimendan has a vasodilatory effect, if administered in high and uniform doses, it could result in drastically reduced blood pressure levels and arrhythmias in patients that may have underlying heart disease. It was found that this was present in over 60% of the patients in SURVIVE. The major take away points from the failure of these trials is that high initial infusion of levosimendan should be avoided, and that pre-existing conditions such as hypovolemia and low blood pressure need to be ruled out prior to beginning treatment (Follath *et al*., 2009).

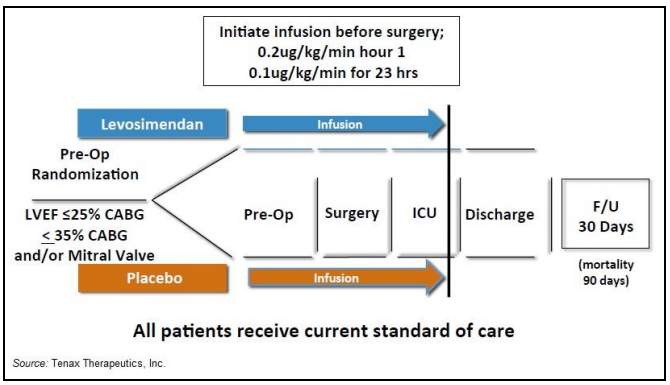
We believe that Tenax has taken levosimedan's past, including successful and unsuccessful trial details, into serious consideration, especially in the design and execution of the Phase 3 LEVO-CTS trial for cardiac surgery patients with LCOS. We believe that this is imperative in order for Tenax to advance levosimendan successfully.

Levosimendan in Cardiac Surgery: Ongoing Phase 3 LEVO-CTS Trial

As mentioned above, levosimendan is currently being developed in North America by Tenax. Levosimendan has been granted Fast Track status by the U.S. Food and Drug Administration (FDA), which approved Tenax's Phase 3 LEVO-CTS clinical trial protocol under a Special Protocol Assessment (SPA) in 2012.

In 2014, Tenax initiated "*Levosimendan in Patients With Left Ventricular Systolic Dysfunction Undergoing Cardiac Surgery On Cardiopulmonary Bypass*" (LEVO-CTS) Phase 3 trial to evaluate the efficacy of levosimendan in the reduction of the incidence of morbidity and mortality in cardiac surgery patients at risk of LCOS when levosimendan is administered before and during cardiopulmonary bypass. The study looks at the 30-day composite event rate of all-cause death, perioperative myocardial infarction, the need for dialysis, or the use of mechanical assist (intra-aortic balloon pump [IABP], left ventricular assist device [LVAD], extracorporeal membrane oxygenation [ECMO]) in patients with left ventricular systolic dysfunction (reduced ejection fraction) preoperatively undergoing cardiac surgery via cardiopulmonary bypass. LEVO-CTS is a double-blind, randomized, placebo-controlled trial. We believe it is important to point out that the well-renowned Duke Clinical Research Institute (DCRI) is conducting the trial, and helped design the Phase 3 protocol.

As of the September 14, 2015, 62 out of 70 total cardiac surgical sites across the U.S. were activated. Patient enrollment began in September 2014, and as of September 14, 2015, a total of 180 patients were enrolled. We believe that the goal is to enroll approximately 760 patients undergoing coronary artery bypass graft or mitral valve surgery who are at a risk of developing LCOS. We believe that management is focused on increasing enrollment efforts, and continues to take numerous steps in order accelerate the process. For instance, these efforts include identifying additional sites for the trial by expanding to Canada, increasing communication with current clinical sites by hiring two field based associates who will be in direct contact with the sites, and submitting a protocol amendment to the FDA to adjust inclusion criteria (adjusting EF from 25% to 35%, and no longer excluding COPD patients) to possibly increase the number of patients that quality for this trial. As per management, a response from the FDA regarding the protocol amendment is expected at some point in September 2015.



The trial has two arms, and in the experimental arm, patients will be administered 0.2 µg/kg/min of levosimendan for the first hour, followed by 0.1 µg/kg/min of levosimendan for an additional 23 hours (with infusion being initiated prior to surgery), while in the placebo comparator arm, patients will be given 0.2 µg/kg/min of placebo for the first hour, followed by 0.1 µg/kg/min of placebo for an additional 23 hours (*above*). We would like to mention that endpoints of the trial were selected based on available clinical scientific evidence. Cardiac surgery patient criteria include: (1) Isolated CABG LVEF ≤ 25%; (2) ≤ 35% CABG and/or mitral valve surgery; and (3) EF ≤ 35% CABG and aortic valve surgery (which is a recent amendment, and is expected to increases patient pool by 25%). The inclusion parameters above are intended to enhance the event rate and treatment effect. As per Tenax, a 32% event rate appears conservative, and a 35% treatment effect is conservative relative to 60-80% relative risk reduction in low EF clinical trials (DCRI Meta-analysis; Levin *et al.*, 2012; Baysal *et al.*, 2014).

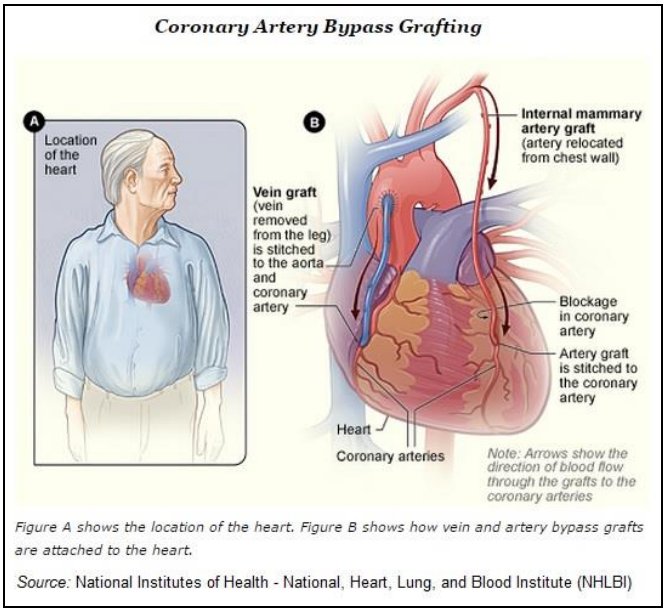
Co-primary endpoints in the trial include: (1) "Dual": death or mechanical assist (IABP, LVAD) through day 5, $p<0.04$ sufficient, and (2) "Quad": death (through day 30), perioperative non-fatal MI (day 5), renal dialysis (day 30), or mechanical assist (day 5), $p<0.01$ sufficient, while secondary endpoints, which also intend to show the pharmacoeconomic benefit of the drug, include duration of ICU/CCU stay following surgery, and the incidence of LCOS. The safety endpoint is all-cause mortality through day 90, and since this an event-driven trial, there will be an event rate check at 200 patients with interim analysis at 50% and 70% total events to ensure anticipated event rate. The trial may be stopped for profound efficacy in "dual" endpoint.

It appears that low left ventricular ejection fraction (LVEF) cardiac surgery patients represent a high-risk population who experience a higher incidence of LCOS and more severe outcomes. Based on levosimendan's established clinical profile that has demonstrated potential benefits in LCOS, we see the potential in the drug to reduce mortality and morbidity in cardiac surgery patients at risk for LCOS, as well as lowering hospital related / pharmacoeconomic costs. In our opinion, the data that is available appears to be promising; however we do believe larger multi-site randomized controlled trials, like LEVO-CTS, with the proper dosage protocols in place will offer much needed data to confirm the benefit of levosimendan in cardiac surgery patients. We view levosimendan as potentially being able to address an unmet need with the dual value proposition mentioned above.

As per management, the FDA has provided guidance that a single successful trial will be sufficient to support approval of the drug for this particular indication. The LEVO-CTS data readout is expected during the second half of calendar year 2016, and we are looking forward to reviewing the results once available. From start to finish, we believe that the trial will cost approximately $18 to $20 million. If all goes well, the company plans to request FDA Priority Review (6 months), and we think approval could occur at some point during the first half of calendar 2017. We are very much interested in watching the Tenax story unfold.

The Market Opportunity: Narrowing in on the Cardiac Surgery Market

When addressing certain advanced conditions of the heart, surgical intervention is often required, with the goal to improve quality of life and chance of survival in addition to reducing symptoms. According to the NHLBI, the most common type of heart surgery in adults in the U.S. is coronary artery bypass grafting (CABG), where a healthy artery or vein from the body is connected to a blocked coronary artery in order to improve blood flow to the heart (*below*).



Based on our research, we believe that CABG procedure volumes have declined in the U.S. since the late 1990s, and furthermore, the risk-adjusted mortality for CABG has also declined over the past decade (Mozaffarian *et al*., 2015). After consulting several sources, including the most recent Society of Thoracic Surgeon's (STS) Database (*below*), we believe that the initial market opportunity in the U.S. for levosimendan (as per what the company is evaluating in LEVO-CTS) would include cardiac surgery patients requiring cardiopulmonary bypass as well as valvular surgery and congenital heart surgery patients resulting in approximately 320,000 procedures. STS has over 7,000 members across 90 countries, and was founded in 1964 as an international nonprofit organization in order to represent cardiothoracic surgeons, and other members of the cardiothoracic surgical team. We would like to mention that although isolated CABG procedures make up the largest portion of the STS database and seem to be declining, overall cardiac procedure rates seem to be increasing slightly year-over-year.

Adult Cardiac Surgery Database
Executive Summary
10 Years

STS Period Ending 03/31/2015

Duke Clinical Research Institute

2015 is a partial year: Jan 2015 - Mar 2015

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Yearly Number of Sites in Analysis	797	875	949	982	1,014	1,032	1,043	1,052	1,050	938
Yearly Overall Procedure Count	267,860	273,864	287,964	295,774	291,410	279,007	274,969	282,665	281,807	65,778
Major Procedures										
Isolated CABG	161,733	164,340	168,027	167,329	160,819	149,649	146,450	147,641	146,578	34,539
Isolated Aortic Valve Replacement	16,957	18,730	21,376	24,501	25,621	27,257	28,768	30,633	29,552	6,981
Isolated Mitral Valve Replacement	4,498	4,522	4,845	5,336	5,495	5,877	6,303	6,647	6,961	1,546
Aortic Valve Replacement + CABG	15,540	15,879	17,536	18,823	18,344	18,214	18,370	18,568	18,230	4,131
Mitral Valve Replacement + CABG	2,648	2,582	2,576	2,589	2,446	2,322	2,383	2,434	2,607	621
Aortic + Mitral Valve Replacements	1,163	1,285	1,317	1,503	1,468	1,609	1,661	1,773	1,884	416
Mitral Valve Repair	5,092	5,424	6,155	6,817	7,301	7,835	8,395	8,814	8,787	2,125
Mitral Valve Repair + CABG	4,838	4,854	5,177	4,898	4,759	4,596	4,708	4,791	4,252	978
Not Classified Above	55,391	56,248	60,955	63,978	65,157	61,648	57,931	61,364	62,956	14,441
Incidence of Other Procedures										
Pulmonic Valve	447	454	505	543	543	472	547	539	549	118
Tricuspid Valve	5,965	6,090	6,903	7,369	7,625	8,203	8,649	9,316	9,892	2,272
Ventricular Assist Device	1,134	1,198	1,512	1,863	2,434	3,202	3,544	4,159	4,631	1,062
LVA - Left Ventricular Aneurysm Repair	1,189	1,139	1,041	925	831	790	781	702	664	136
VSD - Ventricular Septal Defect Repair	618	575	634	625	637	672	700	650	741	168
ASD - Atrial Septal Defect Repair	3,158	3,372	3,940	4,285	4,230	4,687	5,194	5,418	5,779	1,241
Batista	38	47	47	34	42	17	-	-	-	-
Surgical Ventricular Restoration	515	436	404	303	193	208	198	209	209	45
Congenital Defect Repair	1,697	2,073	1,821	1,579	1,544	1,564	1,702	1,665	1,277	215
Transmyocardial Laser Revascularization	3,208	2,497	2,387	2,033	2,011	1,755	1,723	1,489	1,449	313
Cardiac Trauma	293	291	335	297	287	280	289	267	260	58
Cardiac Transplant	978	1,031	1,121	1,226	1,367	1,356	1,385	1,579	1,675	315
Arrhythmia Correction Surgery	1,409	1,275	1,370	1,211	1,159	1,039	921	940	848	158
Atrial Fibrillation Correction Surgery	14,978	15,074	16,013	16,593	16,825	17,568	21,176	24,621	19,254	2,424
Aortic Aneurysm	9,553	10,138	11,734	13,127	13,947	12,882	11,745	12,486	12,400	2,877
Ascending Aorta	7,896	8,501	10,024	11,431	12,140	10,633	9,149	9,759	9,839	2,391
Aortic Arch	2,298	2,415	2,762	3,183	3,501	3,155	2,854	3,098	3,185	768
Descending Aorta	1,054	1,088	1,122	1,154	1,281	1,047	754	769	850	212
Thoracoabdominal Aorta	630	571	670	631	708	660	652	740	648	112
Carotid Endarterectomy	2,211	2,042	2,081	1,884	1,775	1,581	1,396	1,385	1,304	328
Other Vascular	1,365	1,199	1,470	1,566	1,500	1,383	1,253	1,302	1,362	318
Other Thoracic	1,631	1,605	1,795	1,663	1,663	1,556	1,599	1,679	1,699	406

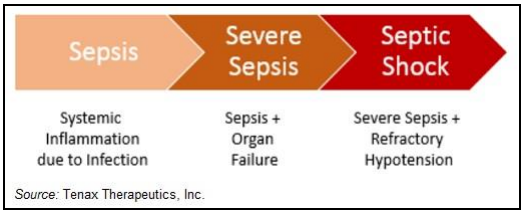
Source: Duke Clinical Research Institute & The Society of Thoracic Surgeons: Adult Cardiac Surgery Database - Executive Summary, Ending 3/31/15

We believe that the market opportunity for levosimendan is quite large, as the drug is proposed to treat patients undergoing cardiac surgery at risk for LCOS, and a potential indication in septic shock. We believe that there is data that does support the use of levosimendan in other critical care indications, especially ones that require inotropic support, but it is still early for us to asses those settings. However, management does believe that there may be an opportunity in the future to expand to other indications such as non-cardiac surgical indications with heart disease; cardiogenic shock post-acute myocardial infarction; and severe acute decompensated heart failure.

Levosimendan in Septic Shock

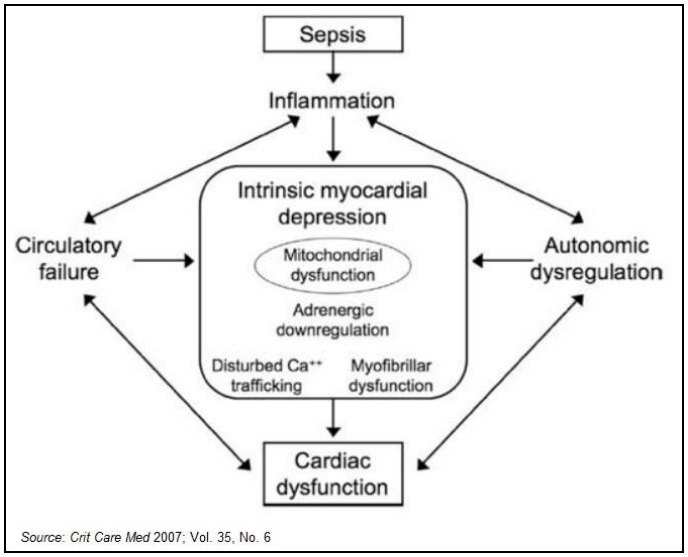
Background on Sepsis

Septic shock is a life-threatening condition that causes blood pressure to fall to dangerously low levels, resulting in compromised blood flow to vital organs, such as the liver and kidney. It is an overwhelming immune response to an infection, typically bacterial, but also to those caused by fungi, parasites, or viruses. The infection itself is not the cause of the symptoms associated with sepsis. Instead, it is the vast amounts of pro-inflammatory cytokines released by the immune system that causes symptoms such as fever, elevated heart rate, hyperventilation, altered mental state, and low blood pressure.



During the course of an infection, the immune system is responsible for recognizing invading pathogens. Part of this process involves the release of cytokines to stimulate inflammation and other immune system cells to aid in the fight against the invading pathogen. For reasons that are not well understood, these immune cells sometimes release more cytokines than are necessary. This results in making blood vessels slack and permeable, thereby reducing

blood pressure and allowing the fluid component of blood to seep into surrounding tissues. The blood component is left behind and forms small clots in tiny blood vessels, which decreases the amount of oxygen that can reach major organs. This is the danger point, as patients who have progressed this far have reached the later stages of the disease. At this point, confusion sets in, the heart begins beating erratically, the kidneys and other major organs begin to fail, and the patient's blood pressure cannot be raised. Thus far there is no cure for sepsis, other than palliative care, typically in an intensive care unit. Patients meet the criteria for septic shock if they have sepsis with persistent hypotension and perfusion abnormalities despite adequate fluid resuscitation.



The condition of sepsis has been known for an extremely long time, however it has always been difficult to define and diagnose. For the past century, sepsis has been defined as the systemic host response to an infection (Riedemann *et al*., 2003). Sepsis was originally thought to be associated with the presence of bacteria in the bloodstream (bacteremia). However, many patients present with symptoms of sepsis and do not have an active bacterial infection in their blood. Based on the lack of a consensus definition, in 1991 a conference was convened to focus on a way to clinically define sepsis. The outcome of this meeting was a joint publication by the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) with consensus definitions of sepsis (ACCP/SCCM, 1992). Importantly, this publication introduced the term systemic inflammatory response syndrome (SIRS), for which no definable presence of bacterial infection is required. In addition, the terms "severe sepsis" and "septic shock" were introduced to differentiate the different stages of sepsis.

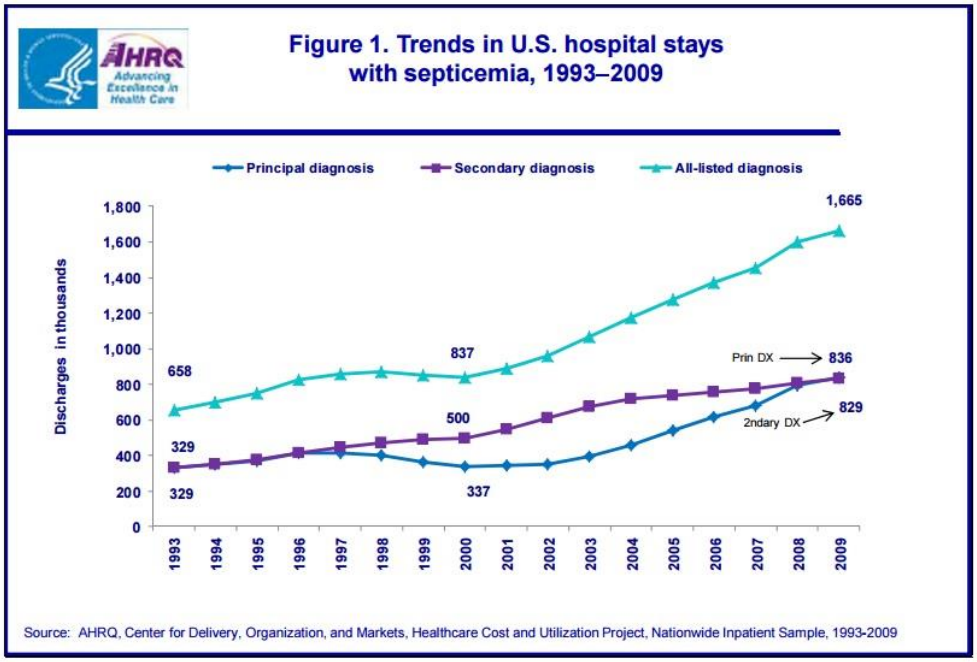
ACCP/SCCM named condition	Defining criteria
SIRS	Core body temperature >38°C or <36°C HR ≥90 bpm Respirations ≥20/min (or $PaCO_2$ <32 mmHg) WBC ≥12,000/μl or ≤4000/μl or >10% immature forms
Sepsis	At least two SIRS criteria caused by known or suspected infection
Severe sepsis	Sepsis with acute organ dysfunction (including hypoperfusion and hypotension) caused by sepsis
Septic shock	Sepsis with persistent or refractory hypotension or tissue hypoperfusion despite adequate fluid resuscitation
MODS	The presence of organ dysfunction in an acutely ill patient such that homeostasis cannot be maintained without intervention.

ACCP: American College of Chest Physicians; HR: Heart rate; MODS: Multiple organ dysfunction syndrome; $PaCO_2$: Partial pressure of carbon dioxide in the blood; SCCM: Society of Critical Care Medicine; SIRS: Systemic inflammatory response syndrome; WBC: White blood cell. *Source*: Martin, 2012

Incidence of Sepsis

The consensus definitions of sepsis (*above*) have allowed for epidemiological studies to be conducted on the incidence of sepsis, which occurs in approximately 2% of all hospitalizations in developed countries. There has been more attention paid to the incidence of severe sepsis and septic shock, with published reports showing an incidence of severe sepsis of 50 to 100 cases per 100,000 people in the population (Danai *et al*., 2005). Trends

indicate that there is a growing incidence of severe sepsis in the United States, and there are over 1.5 million U.S. inpatient hospital stays associated with a primary or secondary diagnosis for septicemia annually (*below*) (AHRQ, 1993-2009).



It is estimated that there are 1 million cases of sepsis in the United States each year (Martin, 2012; NCHS/CDC, 2011). Interestingly, significant longitudinal changes in the incidence of sepsis have been noted over the past few decades, with the incidence of sepsis in hospitalized patients growing by 8.7% per year (Martin *et al*., 2003). This increase in the incidence of sepsis is not just confined to the U.S., but has also been noted in the U.K. and Australia (Harrison *et al*., 2006; Finfer *et al*., 2004). Furthermore, management estimates that the annual incidence of septic shock in the U.S. is over 450,000 patients per year based on ICD-9 coding data. Average mortality rates are often reported to be 20-30% range, however mortality rates can exceed 50% in some high risk patients (Leligdowicz *et al*., 2014). Septic shock is not only associated with high mortality, but also high morbidity and hospital and critical care costs.

There are a number of patient-specific factors that affect the incidence of sepsis and risk factors that predispose certain individuals to developing sepsis. A variety of comorbid conditions will significantly increase an individual's risk of developing sepsis, including HIV, cancer, and diabetes (Danai *et al*., 2006). Race, ethnicity, and gender have also been shown to result in differential risks for developing sepsis, with males and non-Caucasians having the highest risk (Martin *et al*., 2003).

Treatment and Management of Sepsis

Prompt diagnosis of sepsis is critical for a positive outcome. A 2006 study reported that for a septic patient the chance of dying goes up by 7.6% for every hour that goes by without treatment (Kumar *et al*., 2006). Effective sepsis treatment relies on the use of intravenous fluids, antibiotics, drainage of infected sites, and proper support for organ dysfunction.

Early goal directed therapy is an approach to the management of severe sepsis during the first six hours after diagnosis. This method was first introduced by Dr. Emanuel Rivers in 2001 and relies on intensive monitoring and aggressive management of perioperative hemodynamics (Rivers *et al*., 2001). When applied to the treatment of sepsis, the approach involves adjustments in cardiac preload, afterload, and contractility. What this means is that intravenous fluids are titrated in response to heart rate, blood pressure, and urine output. Different types of fluids have been shown to be more advantageous than others, with crystalloid solutions and albumin performing better at reducing mortality in comparison to hydroxyethyl starch (Rochwerg *et al*., 2014).

In 2013, revised international guidelines for the treatment of sepsis were published (Dellinger *et al*., 2013). The guidelines call for diagnostic tests to be performed within the first three hours of diagnosis including measurement of serum lactate and blood cultures before initiating antibacterial treatment, so long as it does not delay

antimicrobial treatment for more than one hour. For every one hour delay in the use of antibiotics, a patient's risk of dying increases by 6% (Soong *et al*., 2012). Additional means of treatment include the use of anti-hypotensive agents to raise the patient's blood pressure and tracheal intubation if the patient's oxygen level remains low.

Sepsis patients are typically considered to be high risk for morbid complications and death. A rough percentage of patients who ultimately die from sepsis are as follows, broken down by the consensus definitions:

Sepsis: 10-20%
Severe sepsis: 20-50%
Septic shock: 40-80%

Thankfully, the overall mortality rate for those with sepsis has been declining, with the rate falling from 30% of sepsis patients in the 1980s and 1990s to 20% of patients within the past decade (Martin *et al*., 2003). Regardless, the number of individuals who die each year from sepsis (~200,000 in 2007) is similar to the number who dies from acute myocardial infarction. Sepsis is the 10th leading cause of death in the United States. In the United States, sepsis accounts for more deaths than the number of deaths from AIDS, breast cancer, and prostate cancer, combined. We view septic shock as an area of high unmet medical need and believe that if Tenax can demonstrate a clinical improvement in mortality, morbidity, and length of hospital/ICU stay, levosimendan could be adopted as a standard of care therapy for treating life-threatening septic shock.

Scientific Evidence that Supports Levosimendan in Septic Shock

A recent meta-analysis (Zangrillo *et al*., 2015) that examined levosimendan in regards to the reduction of mortality in severe sepsis and septic shock patients as compared to standard inotropic drugs, such as dobutamine. The meta-analysis examined randomized trials in sepsis and septic shock, and analyzed seven studies that included a total of 246 patients. It was found that levosimendan was associated with significantly reduced mortality (59/125 or 47%) vs. standard inotropic therapy (74/121 or 61%).

Levosimendan's proposed mechanism of action suggests the potential of the drug to be evaluated in cases of septic shock. The observed vasodilatory effects of levosimendan could lead to potential cardiac and hemodynamic improvements in these cases with a potential positive impact on microvascular blood flow and protection of mitochondria from oxidative injury and broader organ protection effects by the opening of potassium channels.

Levosimendan in Septic Shock: Phase 2b LeoPARDS trial

In August 2014, Tenax announced a collaboration with the Imperial College of London to provide an additional $0.5 million funding for the ongoing Phase 2 LeoPARDS trial ("Levosimendan for the Prevention of Acute oRgan Dysfunction in Sepsis") in the UK evaluating levosimendan in sepsis. The trial is being managed by NIHR, and led by the Imperial College of London, with Tenax support helping to accelerate the enrollment process. The trial is designed to evaluate if levosimendan reduces the incidence and severity of acute organ dysfunction in adult patients with septic shock, the effect of the drug on organ function, in addition to evaluation of the drug's safety profile in sepsis. The trial was initiated in the first quarter 2014, and as of September 15, 2015, 430 out of 516 patients were enrolled.

LeoPARDS is a randomized, double-blind, placebo-controlled multi-center trial based on previous smaller studies that have evaluated levosimendan as it pertains to sepsis. Adult patients with suspected or confirmed infection and 2 or more SIRS (systemic inflammatory response syndrome) criteria [fever or hypothermia: temp >38°C/100.4°F or <36°C/96.8°F; tachycardia: heart rate >90bpm; tachypnea or need for mechanical ventilation: respiratory rate >20 or PaCO2 <32mmHg; leukocyte count (>12,000cells/mm3, <4000cells/mm3, or >10% immature band forms)] who are dependent on vasopressors to maintain their blood pressure are eligible for LeoPARDS enrollment. Once eligibility criteria are met there is a 24 hour window for recruitment to the trial, and enrolled patients are randomized to receive either levosimendan (0.05 to 0.20µg/kg/min) or placebo for 24 hours in addition to the standard of care.

The primary outcome measure will be the mean SOFA (sequential organ failure assessment) score on ICU after randomization between treatment groups. Secondary outcomes that are also being evaluated include oxygen delivery (ScvO2) & cardiac output; incidence & duration of renal failure (AKIN criteria); serum bilirubin; time to extubation; 28-day, hospital and three & six-month survival; ICU and hospital length of stay, and ICU-free days; duration of renal replacement therapy; and days free from catecholamine therapy.

LeoPARDS data is expected in early calendar year 2016. The data collected from the LeoPards trial will help guide Tenax regarding the future plans for U.S. development. We believe that positive LeoPARDs data could support an

NDA filing. As an aside, in November 2014, Tenax had a meeting with the FDA regarding the development of levosimendan in septic shock, and received guidance on how LeoPARDS data might be analyzed to support regulatory filing. As per management, Tenax has developed a statistical analysis plan (SAP) with the Imperial College of London and plans to submit it to the FDA by the end of the third quarter of 2015. We look forward to receiving more updates on the clinical and regulatory path forward in the near future. If all goes well, we believe that a Phase 3 trial could commence in late 2016. If the data is positive, we believe that Tenax will plan to file an NDA in late 2016.

On September 10, 2015, Tenax announced a partnership with Sepsis Alliance, a North American nonprofit patient advocacy organization that promotes sepsis awareness and treatment. As part of the partnership, Tenax will be the second Lead Sponsor of Sepsis Alliance's Sepsis Challenge National Events program during the remainder of 2015 and 2016, and will be a sponsor at the Sepsis Heroes event, scheduled to take place in on September 17, 2015 in New York City.

Intellectual Property Portfolio

Since levosimendan is not yet approved in the U.S., we believe that the approval as an N.C.E. (new chemical entity) should offer five years of exclusivity through calendar year 2022 if we estimate a calendar year 2017 approval date. Tenax has several product patents in place that are expected to be listed in the Orange Book post approval (*below*), and are eligible for the 5-year Hatch Waxman extension, potentially extending exclusivity into 2025, with a possible 6-month pediatric extension option. Overall, we believe there is a low risk for generic competition through fiscal year 2025.

US Patent 6,943,164 - Pharmaceutical solutions of levosimendan - expires 2020

US Patent 6,730,673 - Pharmaceutical solutions of levosimendan - expires 2020

Financial Summary & Capital Structure

On September 14, 2015, Tenax reported financial results for the first quarter fiscal year 2016 ended July 31, 2015. Tenax reported a net loss of $3.0 million or $0.11 per share for the first quarter fiscal year 2016, compared to a net loss of $2.2 million, or $0.08 per share in the same period in 2015.

Total operating expenses for the three months ended July 31, 2015 were $3.1 million compared to $2.4 million in the prior year. Research and development expenses for the first quarter fiscal year 2016 were $1.7 million, compared to $1.0 million in the same period in fiscal 2015. The increase was primarily due to increases in consulting and personnel costs, and costs related to the Phase 3 LEVO-CTS trial. General and administrative expenses for the first quarter fiscal year 2016 were $1.4 million, which was approximately the same for the same period in fiscal 2015. We expect to see quarterly R&D increases as Phase 3 LEVO-CTS progresses through the remainder of calendar year 2015 and into 2016

As of July 31, 2015, Tenax had $43.9 million in cash, including the fair value of its short and long term marketable securities, compared to $48.1 million at April 30, 2015. We believe that Tenax has enough cash to fund activities through calendar year 2017, which should be sufficient to fund completion of Phase 3 LEVO-CTS trial.

Risks to Consider

Clinical Risk: Although there is existing data that supports the potential for levosimendan to reduce mortality and morbidity in heart failure/surgery settings, and although the drug is approved in over 60 countries, levosimendan has not yet met FDA requirements for approval as Phase 3 LEVO-CTS is yet completed. In general, there is low probability of success of novel therapeutics to enter the market, and there is always a possibility that the drug could fail in the Phase 3 trial, which would greatly affect our valuation.

Regulatory Risk: Levosimendan must obtain FDA approval prior to commercialization, and although we believe that the approval requirements will be generally forthright, regulatory decisions can often be unpredictable. Regulatory bodies may require additional studies to be performed if any safety or efficacy concerns arise from the Phase 3 SPA-designed LEVO-CTS trial. If this occurs, delays or refusal to approve levosimendan could impact Tenax's

ability to continue funding development and/or continued operations, in addition to delaying the generation of revenues.

Commercialization Risk: We believe that the success of Tenax will depend largely on commercializing levosimendan in a timely fashion upon approval. In our opinion, Tenax will need to expand its operations by building up a specialized sales force targeting cardiac surgeons. Since Tenax does not have any experience promoting drugs in this class, it will take additional effort to bring levosimendan awareness to physicians and patients.

Manufacturing Risk: Since Tenax relies on Orion to manufacture its product, any issues that arise with the manufacturer to supply product would negatively impact Tenax's ability to develop and commercialize its products. This would cause delays in generating meaningful revenues.

Intellectual Property Risk: The U.S. Compound Patent (5,569,657) for levosimendan expired in 2013. Although we believe that being a N.C.E will grant levosimendan exclusivity for five years, and offer protection against generics entering the market, changes in U.S. laws or the ability of a generic drug maker to challenge the existing product patents that Tenax plans to list in the Orange Book may impede Tenax's ability to advance levosimendan, negatively impacting the penetration and sales of the drug. This could also affect the future ability of levosimendan to gain approval for other clinical indications, such as for septic shock.

Financing Risk: Tenax is not yet a profitable company. Although the company has cash on hand, we believe it will need to raise additional capital before levosimendan commercialization. If Tenax is unable to raise capital, this could drastically limit the company's operations.

MANAGEMENT PROFILES

John P. Kelley – Chief Executive Officer

John P. Kelley joined Tenax as Chief Executive Officer in November 2013, and has served as a director since December 2013. Prior to joining the company, Mr. Kelley co-founded Phyxius Pharma, Inc. and held the positions of Chief Executive Officer and Director from 2010-2013. Prior to Phyxius, Mr. Kelley served as President and Chief Operating Officer of The Medicines Company, a provider of medical solutions to hospitals, from 2004-2009 and as a director from 2005-2009. Prior to The Medicines Company, Mr. Kelley held a series of positions at Aventis Pharmaceuticals, Inc. an international pharmaceutical company. From 2003-2004, Mr. Kelley served as Senior Vice President, Global Marketing and Medical at Aventis, where he was accountable for worldwide brand management of Aventis' core strategic brands and managed strategic alliances with partner companies. From 2002-2003, he served as Senior Vice President, Strategic Risk Officer for Aventis, advising the Management Board and Chief Executive Officer. From 2000-2002, Mr. Kelley served as Vice President, Head of Strategic Development of Aventis where he was responsible for leading the strategic planning process of the pharmaceutical division of Aventis as well as merger and acquisition activity. Prior to the formation of Aventis, he served as a Vice President, Commercial Director, U.S. at Hoechst Marion Roussel, Inc., a life sciences firm focused on pharmaceuticals and agriculture, from 1998-1999 and Mr. Kelley served as Vice President of Marketing of Hoechst Marion Roussel from 1995-1998. Mr. Kelley currently serves on the Board of Directors of Acorda Therapeutics. Mr. Kelley received a B.S. degree in Biology from Wilkes University and an M.B.A. from Rockhurst University.

Michael B. Jebsen – Chief Financial Officer

Michael B. Jebsen was named Interim Chief Executive Officer in August 2011, while retaining his role as Chief Financial Officer and Treasurer. He joined Oxygen as the Accounting Manager in April 2009 and was elected CFO in August 2009. Before joining Oxygen, he was an auditor with Grant Thornton, LLP from 2003-2005 and from 2008- 2009. In addition, he held various positions, including Chief Ethics Officer, Senior Internal Auditor, and Senior Financial Analyst with RTI International, a non profit research and development organization, from 2006 -2008. Mr. Jebsen holds a Master of Science in Accounting from East Carolina University and is a certified Public Accountant, licensed in North Carolina.

Paula Bokesch, M.D. – Chief Medical Officer

Dr. Bokesch has more than 10 years of drug development experience in acute and critical care indications. Most recently she worked for 5 years as a Senior Medical Director for Drug Development at Cubist Pharmaceuticals, where she served within the Company's programs for Daptomycin, pain, acute/critical care and antibiotics. Dr. Bokesch also served as Global Medical Director for Hospira, where she worked in Medical Affairs and Drug Development within the Precedex and acute/critical care programs. She is also a practicing anesthesiologist at St. Elizabeth's Hospital in Boston, as well as an Affiliate Assistant Professor at Tufts School of Medicine. Dr. Bokesch holds an M.D. from the Bowman Gray School of Medicine at Wake Forest University.

Douglas Hay, PhD – EVP of Regulatory Affairs

Dr. Hay has over 27 years pharmaceutical regulatory experience. Prior to joining the company, Dr. Hay was co-founder of Phyxius Pharma, Inc. where he served as Vice President of Regulatory Affairs. Previously, Dr. Hay lead positions in global regulatory affairs at The Medicines Company and Shire Pharmaceuticals. He spent the majority of his career at Bristol Myers Squibb where he advanced to

Vice President, Global Regulatory Sciences. This experience spans drug development (Phase 1-4) in numerous therapeutic areas, including the development of novel biologics and new chemical entities. Dr. Hay's experience has included responsibility for development projects in virtually all major cardiovascular classes, including development/registration programs for Capoten, Monopril, Avapro, Plavix, and Angiomax. Doug received his AB degree in Biology from University of California, Riverside, MS in biology at California State University, Long Beach, and PhD (physiology emphasis) from Northern Arizona University.

Nancy Hecox, J.D. – EVP, Legal Affairs, General Counsel, and Corporate Secretary

Nancy Hecox joined Oxygen as General Counsel in October 2009. She brings over a decade of experience in the pharmaceutical/biotech industry from prior positions with Becton Dickinson, eTrials Worldwide, Quintiles, and DSM Pharmaceuticals. Ms. Hecox holds a BS degree in Communications from the State University of New York and an MBA from East Carolina University. She received her JD degree from North Carolina Central University, graduating cum laude, and is admitted to the North Carolina State Bar.

Doug Randall – EVP of Commercial and Business Operations

Doug Randall has 31 years of pharmaceutical executive experience. Prior to joining the company, Mr. Randall co-founded Phyxius Pharma, Inc. in 2011 where he served as the Chief Commercial Officer. Previously, Mr. Randall served in many senior level executive positions within the pharmaceutical industry, including: Vice President of Commercial Operations at The Medicines Company; Vice President of US Diabetes Marketing at Sanofi-Aventis Pharmaceuticals; and Vice President of Sales at Aventis Pharmaceuticals. Prior to the formation of Aventis Pharmaceuticals in 2000, Mr. Randall served in several senior commercial roles at the former legacy companies (Hoechst Marion Roussel, Marion Merrell Dow, and Marion Laboratories) including: Director of Respiratory Marketing, Director of Cardiovascular marketing, Director of GI/CNS Marketing, Director of Distribution and Pharmacy Markets, and various sales management roles. Mr. Randall started his pharmaceutical career as a sales representative for Marion Laboratories, Inc. in 1982 after earning his B.S. in Pharmacy from the University of Rhode Island.

VALUATION AND RECOMMENDATION

We are initiating coverage of Tenax Therapeutics, Inc. (NasdaqCM: TENX) with a "Buy" rating and a price target of $10.00. Tenax Therapeutics, Inc. is a development-stage specialty pharmaceutical company focused on the identification, development, and commercialization of products for the critical care industry. Tenax's lead product candidate, levosimendan, is currently being studied in a Phase 3 LEVO-CTS trial for low cardiac output syndrome (LCOS) in cardiac surgery patients and a Phase 2 trial for septic shock. Outside of the U.S., levosimendan is currently approved and marketed as Simdax® (levosimendan i.v.) in more than 60 countries for patients with acute decompensated heart failure (ADHF).

The FDA has agreed to Tenax's Phase 3 clinical trial protocol under a Special Protocol Assessment (SPA) and has granted Fast Track designation for levosimendan. As per management, the FDA has provided guidance that a single successful trial will be sufficient to support approval of levosimendan for the indication mentioned above. By way of background, the Fast Track program was put into place under the FDA Modernization Act of 1997 and is a process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need.

The goal of the Phase 3 LEVO-CTS clinical trial is to evaluate if levosimendan administered before and during surgery will reduce the incidence of morbidity and mortality in cardiac surgery patients at risk of LCOS. We believe that LEVO-CTS will most likely be completed during the second half of 2016, and we look forward to reviewing the Phase 3 data during the latter part of 2016. Tenax is also collaborating with the Imperial College of London for the accelerated enrollment and completion of the ongoing Phase 2b LeoPARDS Trial, which aims to evaluate the safety profile of levosimendan and if it reduces the incidence and severity of acute organ dysfunction in adult septic shock patients.

In our opinion, the Tenax development portfolio includes a product candidate that has the potential to address various critical care conditions with high unmet medical need. Currently, there are no approved drugs indicated for the prevention and/or treatment of LCOS. We view levosimendan as a relatively de-risked clinical development opportunity for the indication of LCOS due to the usage of the drug in over 1 million patients outside of North America. There is extensive scientific evidence that supports the use of levosimendan in cardiovascular surgery, with over 35 published clinical trials, meta-analyses, and articles. We also believe that the interest surrounding the drug continues to increase. We also view septic shock as an area of unmet clinical need, as the condition is often associated with high mortality, morbidity and critical care costs. In our opinion, LCOS and septic shock are potential large market opportunities because of the present day high mortality rates and insufficient standard of care practices in these patients. We think there is a demand for superior therapeutics in order to improve patient outcomes in both LCOS and septic shock, in addition to reducing the high costs associated with complications surrounding cardiac surgical patients.

We believe that the Tenax management team has the critical care, clinical, and commercial experience necessary to obtain North American approval of levosimendan. However, we do believe it is taking longer than initially expected to enroll patients in the Phase 3 LEVO-CTS trial. Although the LEVO-CTS trial timeline has been adjusted from when the first patient was enrolled back in September 2014, we are hoping that by focusing efforts on accelerating patient enrollment that the company stays on track with the currently projected second half of 2016 trial completion date, with data readout expected in the latter part of 2016.

Valuation Methodology

We assume approval of levosimendan in the U.S. during calendar year 2017, with product launch later in the year. We believe there is a high probability of approval given the success of the drug outside of the U.S, but will be dependent on positive Phase 3 data. In our opinion, Tenax shares remain significantly undervalued given the potential market opportunity for levosimendan.

For valuation purposes, we utilize a full DCF model based on some reasonable estimates of revenues with the following parameters:

Levosimendan Assumptions:

- *Target Population & Revenue Assumptions:*

We have assumed a current target population of 320,000 cardiac surgical procedures in the U.S., which is predominantly made up of approximately 280,000 major procedures and approximately 25,000 congenital procedures tracked using 2014 data from the Society of Thoracic Surgeon's (STS) Database. We have assumed this surgical patient population is growing in line with historical norms of approximately 0.6% per year, and that about 50% of this group would be the appropriate target for levosimendan.

We believe levosimendan usage can lead to significantly improved outcomes and reduced post-operative hospital costs associated with complications of between $6,000 and $15,000 per patient. In our opinion, this translates into an attractive dual-value proposition in a clinical setting.

We have conservatively estimated that Tenax will be able to charge approximately $2,700 per patient, growing at approximately 2.5% per year. We assume initial penetration of approximately 6% in 2017, growing to a max penetration of 40% by 2024. We have also assumed that levosimendan receives Canadian approval in 2018, which represents an additional 10% of the previous year U.S. revenues.

- *Margin/Expense & DCF Assumptions:*

Our DCF model further makes the following assumptions in regards to expenses:

We have assumed long-term gross margins in the area of 80%. We have assumed operating expenses consisting primarily of R&D of approximately $10 million and G&A expenses of $6.5 million for fiscal year 2016. We assume long-term operating expenses and taxes (after taking into account net operating losses) to run around 12% of sales. We believe there is an 80% probability of success for levosimendan, given the success of the drug outside of the U.S. To take into account the cumulative risks discussed above, we have used a 15% discount rate. Since we are valuing cash flows, we are adding in the cash and marketable securities balance of $43.9 million at July 31, 2015.

Based on our assumptions, we calculate fair value for levosimendan and Tenax to be approximately $310 million. With a fully diluted share count of 34.6 million, this equates to a fair value target price of approximately $10 per share. If levosimendan proves to be successful in the cardiac surgical market, and if the company makes further progress with additional indications, including septic shock, we believe that there is the possibility for significant upside to this valuation.

PROJECTED FINANCIALS

Tenax Therapeutics, Inc. - Income Statement

Tenax Therapeutics, Inc.	2015	Q1 A	Q2 E	Q3 E	Q4 E	2016	2017	2018
Product Revenue	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$25.3	$54.6
YOY Growth	*-100%*							*116%*
Government Grant Revenue	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
YOY Growth	*-81%*				*0%*	*-100%*		
Total Revenues	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$25.25**	**$54.6**
YOY Growth	*-83%*							*116%*
Cost of goods sold	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$5.1	$10.9
Product Gross Margin							*80%*	*80%*
Research and development	$6.7	$1.7	$2.1	$2.6	$3.2	$9.6	$10.1	$10.6
General & administration	$7.2	$1.4	$1.6	$1.8	$1.9	$6.6	$8.0	$8.4
Restructuring & Other Opex	$1.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Finance costs	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Operating Margin							*8%*	*45%*
Interest Income (expense)	($0.0)	($0.0)	$0.0	$0.0	$0.0	($0.0)	$0.0	$0.0
Other expense	($0.8)	($0.0)	$0.0	$0.0	$0.0	($0.0)	$0.0	$0.0
Pre-Tax Income	($14.1)	($3.1)	($3.7)	($4.4)	($5.1)	($16.3)	$2.1	$24.7
Income Taxes Paid	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	**($14.1)**	**($3.1)**	**($3.7)**	**($4.4)**	**($5.1)**	**($16.3)**	**$2.1**	**$24.7**
Net Margin							*8%*	*45%*
Reported EPS	**($0.50)**	**($0.11)**	**($0.13)**	**($0.15)**	**($0.18)**	**($0.57)**	**$0.07**	**$0.80**
YOY Growth	*-81%*	*36%*	*-9%*	*13%*	*25%*	*14%*	*-112%*	*1013%*
Basic Shares Outstanding	28.08	28.12	28.25	28.50	28.75	28.40	29.00	31.00

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

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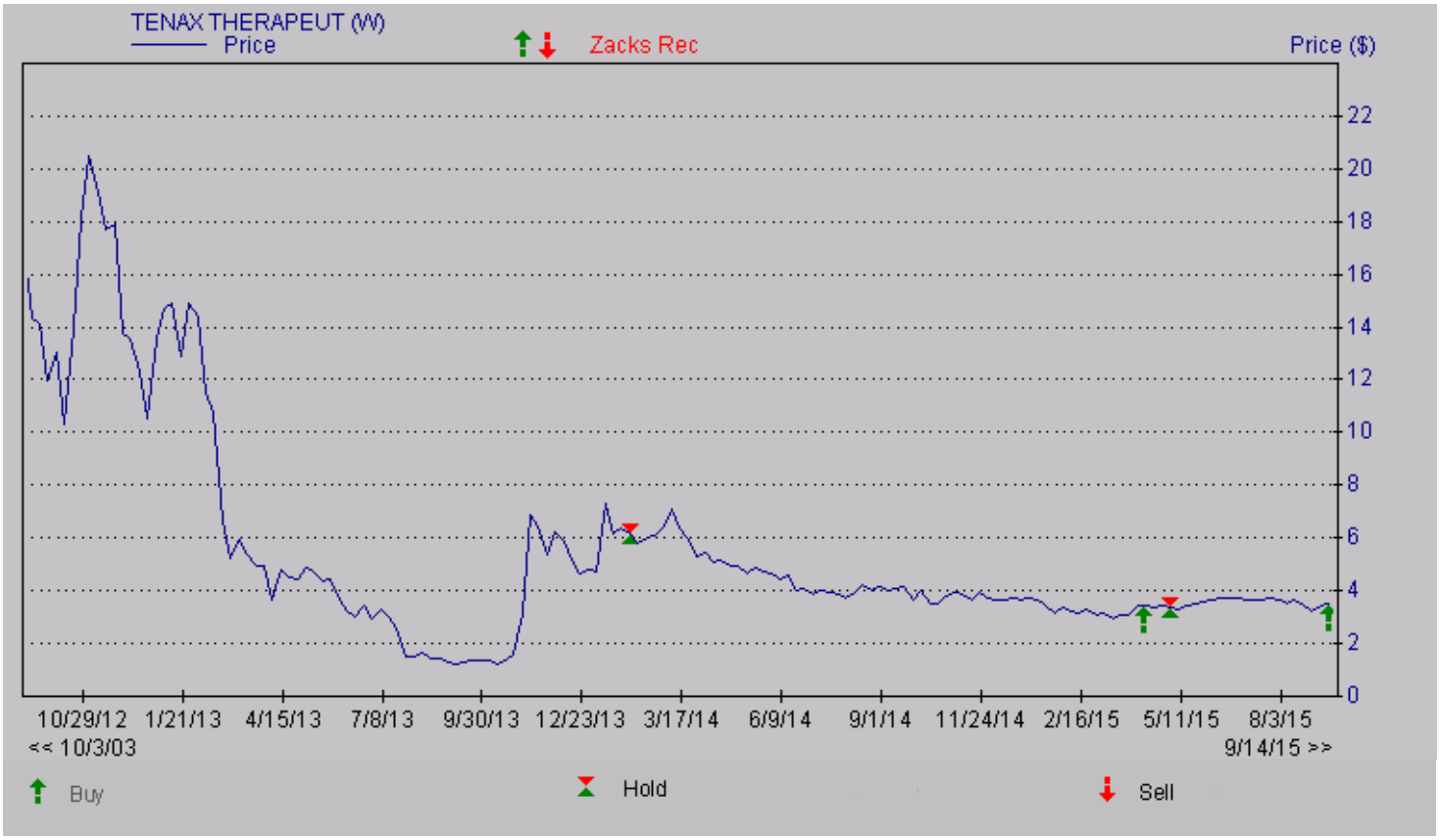
HISTORICAL ZACKS RECOMMENDATIONS



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