Zacks Small-Cap Research

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Tenax Therapeutics, Inc. (TENX-NASDAQ)

New Indication for Levosimendan

Based on our DCF model and a 15% discount rate, TENX is valued at approximately $41.00 per share. We apply a 15% probability of eventual sales of levosimendan in the United States.

Current Price (4/6/18)	$7.67
Valuation	**$41.00**

OUTLOOK

Tenax has licensed the *calcium sensitizer/K-ATP activator* Levosimendan and is currently pursuing approval for an indication in Group 2 Pulmonary Hypertension in the US and Canada. The drug has been approved in over 60 countries with 35 published trials supporting its safety and efficacy and has over 1 million patient exposures.

In January 2018 Tenax announced a new indication for Levo and expects to launch a Phase 2 trial for PH-HFpEF in 3Q:18. This indication has a target population of between 1.5 and 2.0 million patients in the US and there is no existing treatment therapy. TENX will meet with the FDA in 1H:18 to design a Ph2 trial anticipated to begin in 2H:18. Based on trials for similar indications, the duration for Ph2 and Ph3 is expected to yield registrational data by 2023, followed by a 2024 launch of Levo in PH-HFpEF.

Levo has a 16-year history of use in Europe with a substantial volume of literature supporting its safety and efficacy. Given the body of research supporting the use of Levo in pulmonary hypertension and its inotropic and lusitropic effects, there is sufficient evidence to launch a Ph2 trial in PH-HFpEF. Additionally, this is a materially sized market with no current therapy, which provides substantial pricing and penetration opportunity.

SUMMARY DATA

52-Week High	**$15.80**
52-Week Low	**$4.41**
One-Year Return (%)	**-23.9**
Beta	**1.35**
Average Daily Volume (sh)	**348,706**
Shares Outstanding (mil)	**1.43**
Market Capitalization ($mil)	**$11.0**
Short Interest Ratio (days)	**3.45**
Institutional Ownership (%)	**11**
Insider Ownership (%)	**16**
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 2017 Estimate	**N/A**
P/E using 2018 Estimate	**N/A**
Zacks Rank	**N/A**

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

ZACKS ESTIMATES

Revenue
(in millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2017	$0.0 A	$0.0 A	$0.0 A	$0.0 A	$0.0 A
2018	$0.0 E	$0.0 E	$0.0 E	$0.0 E	$0.0 E
2019					$0.0 E
2020					$0.0 E

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2017	-$2.33 A	-$2.12 A	-$0.87 A	-$0.98 A	-$6.27 A
2018	-$1.55 E	-$1.89 E	-$2.24 E	-$2.23 E	-$7.92 E
2019					-$9.56 E
2020					-$9.87 E

WHAT'S NEW

Tenax to Launch Phase II Trial for PH-HFpEF

Following the miss of the LEVO-CTS trial primary endpoints in early 2017, Tenax consulted with the FDA over the summer for guidance on a trial design that would satisfy the statistical significance required to obtain approval for Levosimendan. The favorable trend in 90-day mortality observed in the LEVO-CTS Trial (Levosimendan 4.7% vs. 7.1% Placebo, p=0.123) did provide evidence of good safety and a potential mortality benefit. However, a repeat study with a mortality endpoint was deemed to be too expensive and too lengthy to provide sufficient benefit.

As a result, Tenax maintained rights to a drug approved in Europe but no clear pathway to obtain the same status in the United States. Following an extensive review of existing research and significant input from medical advisors, support was found for using Levosimendan in pulmonary hypertension for patients with heart failure and preserved ejection fraction (PH-HFpEF). In February 2018, Tenax assembled a scientific advisory board of PH experts to confirm the scientific rationale and therapeutic potential for the development of levosimendan in PH-HFpEF Based on feedback from the company's scientific advisors, including recognition of the high unmet need with no other therapy in this indication and the likelihood that Levosimendan can provide a statistically significant result, the decision was made to pursue PH-HFpEF. After a review with the FDA which is currently underway, Tenax will commence a Phase II trial in the second half of 2018.

New Indication for Levosimendan

Levosimendan is a calcium sensitizer and K-ATP channel activator that can improve systolic and diastolic function of the heart as well as provide vasodilatory effects through its ability to relax vascular smooth muscle. This mechanism of action has been shown to lead to important improvements in cardiovascular hemodynamics in previous heart failure studies, including increased cardiac output and reduction in pulmonary capillary wedge pressure which could be very helpful in correcting the reduced cardiac output and pulmonary congestion often seen in PH-HFpEF patients. It is also important to note that Levosimendan has been shown to improve right heart function as well as reduce pulmonary vascular resistance in various patient populations. Improvement in right heart function and reductions in pulmonary vascular resistance could be particularly important to PH-HFpEF patients who often suffer from right heart dysfunction and elevated pulmonary vascular resistance. We believe existing studies provide a compelling rationale to pursue an indication for Levosimendan in PH-HFpEF which has shown potential in multiple unique hemodynamic benefits:

- **Increased cardiac output,**
- **Reduced pulmonary capillary wedge pressure,**
- **Reduced pulmonary vascular resistance, and**
- **Improved right ventricular function**

In addition to the multiple potential clinical benefits of listed above, the drug's unique long-acting metabolite (half-life of 70-80 hours) allows for the convenience of intermittent, rather than continuous IV infusions that are required for approved IV PAH pulmonary hypertension therapies such as Remodulin and Flolan.

Research has been performed examining the impact of Levosimendan on patients with pulmonary hypertension and heart disease. Preliminary data has been supportive of efficacy. Guerrero, in an observational study with 27 high-risk cardiac patients showed that Levosimendan provided a protective role against cardiac, renal and neurological damage for patients undergoing cardiac surgery.[1]

A recent study by Jiang[2] also examined the impact of Levosimendan on PH patients with heart failure. While the target group was similar to the one Tenax seeks to study, it was only a single-arm open label study, with a prospective design where patients served as their own control. Despite the shortcomings of the study, data from the walk test over seven days found a dramatic improvement in results following initial infusion.

[1] Guerrero-Orriach, J.L., et al.; Cardiac, Renal and Neurological Benefits of Preoperative Levosimendan Administration in Patients with Right Ventricular Dysfunction and Pulmonary Hypertension Undergoing Cardiac Surgery: Evaluation with Two Biomarkers Neutrophil Gelatinase-Associated Lipocalin and Neuronal Enolase. Therapeutics and Clinical Risk Management; April 21, 2016.
[2] Jiang, Rong; et al. Efficacy and Safety of a Calcium Sensitizer, Levosimendan, in Patients with Right Heart Failure due to Pulmonary Hypertension. September 2017.

Yet another clinical study conducted by Kleber, et al.[3] observed a heterogeneous population of pulmonary hypertension patients, of which a large subset was attributable to left heart disease. The study found the pulmonary pressures fell following levosimendan infusion, thereby meeting its primary endpoint.

Preclinical work has also been accomplished in an animal model[4] that shows Levosimendan treatment increasing the work of the right ventricle, but without an increase in metabolism. While the study did not address long term safety, it is supportive of Levosimendan improving cardiac output. The article also made the point that the increase in work by the heart will be balanced by pulmonary vasodilation resulting in an unloading of the right ventricle.

The potential for Levosimendan's mechanism of action and the results of the aforementioned studies provide ample evidence to support the launch of a Phase II trial to further evaluate safety, identify an optimal dose and prove the concept.

Pulmonary Hypertension associated with Heart Failure and Preserved Ejection Fraction (PH-HFpEF)

Pulmonary hypertension (PH) is high blood pressure in the arteries supplying the lung. PH is a condition where arterial blood pressure is elevated in the lungs and is frequently associated with severe heart and lung conditions. It is defined as mean pulmonary arterial pressure (mPAP) above 25 mm Hg at rest, secondary to an elevation in pulmonary capillary wedge pressure (PCWP) of greater than or equal to 15 mm Hg. The condition is also defined by a diastolic pressure gradient, or difference between PAP and PCWP, of more than 7 mm Hg. Symptoms of the disease are shortness of breath, dizziness, fatigue, inability to exercise, chest pain, and a fast heartbeat among others. These signs arise due to insufficient oxygenated blood available in the body. PH is more common in females with 69% of the afflicted population suffering, compared to males at 31%.

There are five groups of PH, as classified by the World Health Organization. Group 1, due to the availability of treatment, is most well-known and is also called Pulmonary Arterial Hypertension (PAH); however, it is considered a rare disease. Group 2 is the most common, occurring in about half of all PH patients and is related to patients with left heart disease. Group 3 is PH related to chronic lung disease or conditions that cause hypoxemia. Group 4 results from the obstruction of the pulmonary vascular bed with chronic, organized thromboemboli. Group 5 PH is a heterogenous group that is brought about by several factors.

Exhibit I – PH WHO Groupings[5]

TABLE 2. Clinical classification of pulmonary hypertension	
GROUP 1	Primary pulmonary hypertension: idiopathic, familial, drug and toxin induced (appetite suppressant drugs), rare medical conditions
GROUP 2	Secondary to left ventricular disease: mitral valve disease, left ventricular systolic or diastolic failure.
GROUP 3	Secondary to pulmonary disease or hypoxia: COPD, sleep disordered breathing, obesity hypoventilation
GROUP 4	Secondary to chronic thromboembolism
GROUP 5	Unclear and multifactorial etiologies

[3] Kleber, Franz; et al.; Repetitive Dosing of Intravenous Levosimendan Improves Pulmonary Hemodynamics in Patients With Pulmonary Hypertension: Results of a Pilot Study. Journal of Clinical Pharmacology, 2009;49:109-115 © 2009 the American College of Clinical Pharmacology.
[4] Hansen, M. et al.; Levosimendan improves cardiac function and myocardial efficiency in rats with right ventricular failure; Pulmonary Circulation 2017; 8(1) 1–7
[5] http://bariatrictimes.com/wp-content/uploads/benottitable1-aug13.jpg

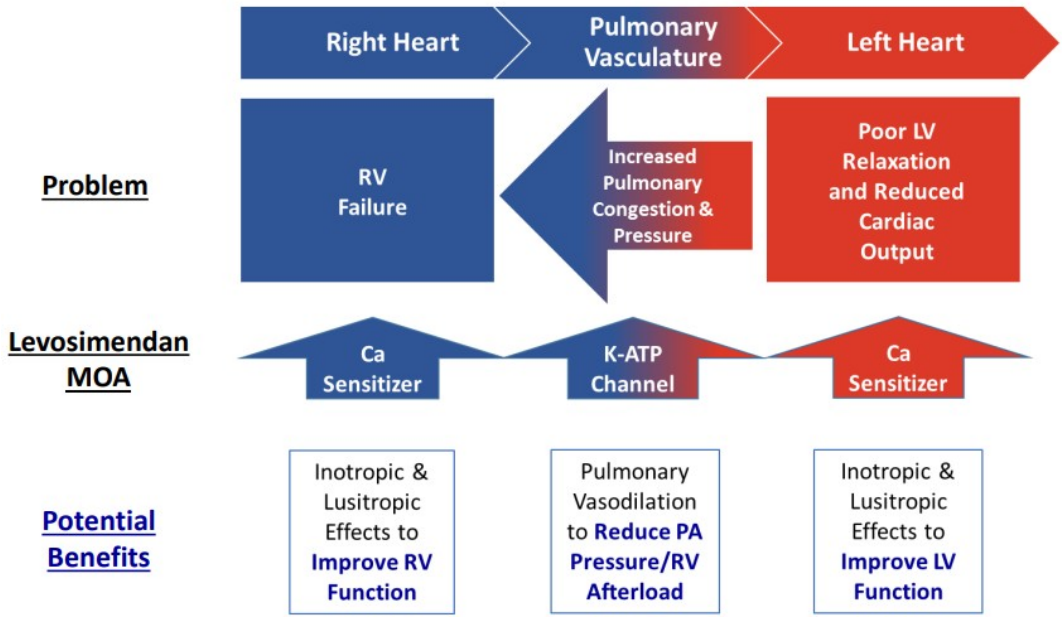
Group 2, or left heart disease PH, occurs in patients with both reduced ejection fraction and with preserved ejection fraction and valvular heart disease. It is thought to be the most common cause of pulmonary hypertension and is associated with high morbidity and mortality. Some research suggests that Group 2 PH may be caused by elevation in left heart pressure either with or without pulmonary arteriolar diseases. In this category, the left side of the heart is unable to pump sufficiently due to heart failure or valve dysfunction. Mitral valve disease may also contribute to Group 2 PH. However, pulmonary blood vessels are normal and undamaged. Group 2 PH is commonly found in patients with heart failure and may occur with or without normal ejection fraction.

There are three identified phenotypes of PH-HFpEF based on clinical presentation including exercise induced diastolic dysfunction (EIDD), overt volume overload and PH right ventricle (RV) failure. EIDD is the most common and presents itself under exertion with few symptoms during rest. Volume overload is characterized by shortness of breath on exertion and is more severe than EIDD. PH RV failure is the most severe phenotype and patients are usually obese, suffer from severe shortness of breath, edema, ascites and are frequently hospitalized. The risk profile of the patient increases as they progress from EIDD to volume overload to PH RV failure.[6]

Elderly patients may have a higher incidence of the disease as shown in a study by Shapiro where 56% of this group were associated with Group 2 PH.[7] It is also associated with obesity and has a higher incidence in Western countries.[8]

The subset of PH-HFpEF patients with right heart dysfunction may benefit from Levosimendan as the drug has been shown to improve right heart failure in various studies. Levosimendan's inotropic and lusitropic effects may allow the right chamber of the heart to to eject more volume to the pulmonary vasculature. In addition, opening of ATP-dependent potassium (K) channels in pulmonary vascular smooth muscle cells may further improve right heart function through reduced pulmonary vascular resistance. Below we provide an exhibit which illustrates the relationships between the mechanism of action and the heart.

Exhibit II – Rationale for Levosimendan in PH-HFpEF Indication



In patients that are diagnosed with HFpEF, higher mortality is associated with PH[9] supporting the need for a treatment. Some of the factors that contribute to poor mortality include increased pulmonary arterial wedge pressure as well as other pressures throughout the pulmonary vasculature.

[6] Shah, Sanjiv, MD., et al.; Phenotypic Spectrum of Heart Failure with Preserved Ejection Fraction, Heart Fail Clin. 2014 Jul; 10(3): 407–418.
[7] Shapiro BP, McGoon MD, Redfield MM; Unexplained pulmonary hypertension in elderly patients. Chest. 2007 Jan; 131(1):94-100.
[8] Hansdottir, Sif; et al. WHO's in Second? A Practical Review of World Health Organization Group 2 Pulmonary Hypertension. Chest. 2013 Aug; 144(2): 638–650.
[9] Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction. A community-based study. J Am Coll Cardiol 2009; 53: 1119–1126.

Symptoms

The primary symptom of PH due to left heart disease (PH-LHD) is an elevated left atrial and pulmonary venous pressure. PH due to left ventricular (LV) systolic or diastolic dysfunction, valvular heart disease, and pulmonary vein stenosis are included in this group. PH due to left heart disease is the most common type of pulmonary hypertension, with more than one-half of those with heart failure thought to have HFpEF.[10]

There are a variety of symptoms related to pulmonary hypertension and heart failure. Obvious signs and symptoms include shortness of breath after minimal physical activity, tiredness, chest pain and a racing heartbeat. This can progress to lightheadedness, fainting and swelling of legs and ankles. Insufficient gas exchange in the pulmonary arterioles may lead to a bluish color in the lips and skin. Upon further examination, other symptoms include pulmonary edema, right ventricle hypertrophy and orthopnea.

Diagnosis

A proper diagnosis of PH and by extension PH-HFpEF, requires catheterization; however, many times the diagnosis is made based on an echocardiogram, Doppler echocardiography or magnetic resonance imaging. A physician will first narrow down the likelihood of the condition with a physical exam and non-invasive diagnostic testing, then perform a right heart catheterization to accurately measure the pressure in pulmonary arteries and measure how well the heart is pumping blood.

Treatment

Currently there is no approved treatment for Group 2 PH, but supplemental oxygen may be given to alleviate symptoms. Some investigational work has also been done in endothelin 1 (ET1), nitric oxide (NO) and phosphodiesterase 5 inhibitors (PDE5Is).[11] ET1 is a potent vasoconstrictor and antagonist therapies were thought to address Group 2 PH. However, several studies conducted failed to show efficacy and some serious adverse events were noted. NO shows some efficacy, but requires constant administration and may involve risk in wedge pressure due to unbalanced pulmonary vasodilation. PDE5Is (such as sildenafil)[12] function by increasing cGMP[13] levels. Early research indicated efficacy for the class for reducing pulmonary pressure in Group 2 PH. A one-year placebo controlled study showed that sildenafil improved life quality, reduced pulmonary artery, wedge and right atrial pressures and right ventricular end-diastolic pressure and dimension;[14] however, larger subsequent studies failed to show a consistent response. PDE5Is have the benefit of relaxing pulmonary vessels and avoiding tachyphylaxis. PH-HFpEF represents an unmet need.

Levosimendan for PH-HFpEF

Levosimendan has several mechanisms that can potentially address the underlying reasons behind PH-HFpEF. The compound is both inotropic and lusitropic, which can alter the force of the heart and allow it to relax more completely. This allows more efficient pumping of blood. The drug also has a vasodilatory effect achieved by opening adenosine triphosphate (ATP)-sensitive potassium channels in vascular smooth muscle. There are a number of publications that have conducted preliminary work evaluating the safety and efficacy of Levosimendan in patients with PH.

Studies Supporting Use of Levosimendan for Pulmonary Hypertension

Work by Guerrero et al. examined whether Levosimendan when administered preoperatively to patients with PH, would have an impact on cardiac, renal and neurological functions. The study assessed cardiac function with echocardiography, renal function with N-GAL[15] levels and the acute kidney injury scale and neuronal damage with neuron-specific enolase levels. Twenty-seven patients were measured at baseline prior to administration of levosimendan using echocardiographic measurements to measure pulmonary hypertension. Patients were measured again, 48 hours post-operatively. Our specific interest here was the impact on pulmonary arterial pressure, which showed a significantly lower value after surgery in the levosimendan arm. On initial measurement, pressures were 58 ±18 mmHg falling to 42 ±19 mmHg 48 hours post-operatively. P-values for the difference in

[10] Hansdottir, Sif; et al. WHO's in Second? A Practical Review of World Health Organization Group 2 Pulmonary Hypertension. Chest. 2013 Aug; 144(2): 638–650.
[11] http://circ.ahajournals.org/content/126/8/975.full
[12] Better known as Viagra.
[13] Cyclic guanosine monophosphate (cGMP) is a cyclic nucleotide derived from guanosine triphosphate (GTP).
[14] https://pdfs.semanticscholar.org/e7ee/9991f571ecbca28eda1fa0870189d2c0cccb.pdf
[15] Neutrophil gelatinase-associated lipocalin (N-GAL) is a protein belonging to the lipocalin superfamily initially found in activated neutrophils. It is a marker of kidney disease.

pressures were equal to 0.001. The article's summary noted Levosimendan's vasodilatory effect and positive impact on contractile force of the cardiac muscle fibers. The drug was described as reducing preload and afterload, improving the efficiency of cardiac work and providing a cardioprotective effect.

A recent study by Jiang[16] also examined the impact of Levosimendan on PH patients with heart failure. While the target population included patients with pulmonary hypertension and right heart failure, the study has several limitations including that it was a small single-arm open-label study, with a prospective design where patients served as their own control. The study enrolled a heterogenous population that did not specifically include HFpEF patients. The study looked at improvement in a walk test over seven days and found a dramatic improvement in results over the seven days following initial infusion.

The study recruited 45 PH patients in a single arm, open-label study with primary endpoints of WHO functional class (FC) and Borg dyspnea scores. Secondary endpoints examined changes in 6-minute walk distance, biochemical markers and right heart structure and function together with adverse events, and incidence of major adverse cardiovascular events. Measurements were taken at baseline and seven days after Levosimendan infusion. The outcome of the study showed that seven of the 13 PH patients in WHO-FC IV improved by one functional class and no patients deteriorated. Borg dyspnea scores moved from 5.0 to 3.0 (essentially severe breathlessness to moderate breathlessness) with a P-value less than 0.001 for the group. No patients were able to complete the walk test of 50 meters at baseline; however, the test results improved significantly to 261 seconds at day seven. Biochemical markers also improved. The takeaway from this study was that Levosimendan showed the potential to improve a variety of PH markers despite not having a randomized, blinded, placebo controlled design.

Yet another study supportive of the pursuit of an indication in pulmonary hypertension is discussed in the Kleber piece, examining the impact of Levosimendan on pulmonary hemodynamics in patients with PH. This study included all PH groups and was a randomized, placebo-controlled, double-blind, parallel-group study undertaken in Germany and Sweden. The study drug was infused over 10 minutes with a loading dose, followed by 50 minutes of continuous infusion. The drug was then readministered every two weeks four additional times. Pulmonary pressures were measured via right heart catheterization.

The primary endpoint was the measure of pulmonary vascular resistance (PVR) after a 24 hour infusion and another measurement of PVR and other hemodynamic variables at 8 weeks. Results showed a statistically significant 12% reduction in PVR over the 24 hour period (p-value = 0.009) and a 13% increase in SvO_2 (mixed venous oxygen saturation with p-value < 0.001). Other metrics were not as statistically significant and most measurements at 8 weeks were far beyond statistical significance.

The study accepted all types of PH patients, however the majority of the participants (67% in levo group and 70% in placebo group) showed signs of right heart failure, suggesting that the efficacy indicated in the study is relevant to this group. In addition, the article notes that a significant proportion of pateints had evidence of left sided heart disease and speculates that the patients suffering from PH due to left-sided heart disease could be a major target population for Levosimendan. However, we note that it is unclear how many of these left-sided heart failure patients were HFpEF patients. While this was a small study and the timing of the measurements not necessarily optimal due to drug half-life and the maximum concentration of the active metabolite, it does provide results that support further examination.

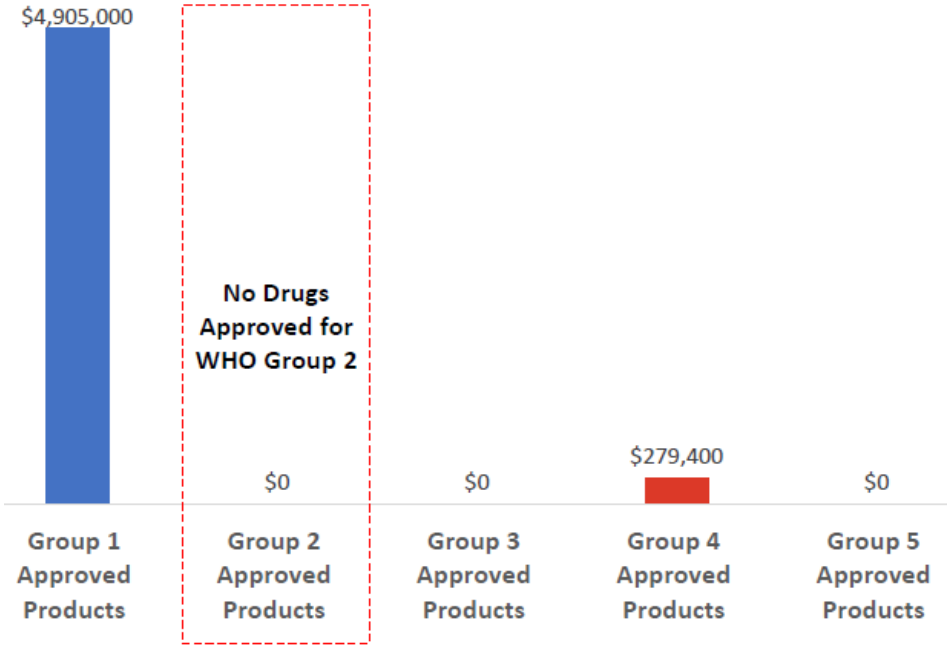
Market Size

PH-HFpEF is an attractive indication as it addresses a large unmet need where mortality is up to 50% in the five years following diagnosis. A successful treatment could improve quality of life, as disease sufferers have difficulty exerting themselves. Further, there are no other treatments for WHO Group 2 PH, which can both allow for expedited development and approval of the drug as well as a strong competitive position in the market. PH is underdiagnosed, which suggests that the number of afflicted could be much larger than we estimate. The condition is found and quantified by employing echocardiography or right heart catheterization, which are infrequently used in the general population. Therefore, the condition is usually not detected until it has progressed to an advanced state and when the heart begins to fail. Due to the infrequent and onerous burden of performing these diagnostic tests, the condition is not widely diagnosed.

Pulmonary hypertension is detected in over 2% of the discharged US population with most of these cases in WHO Group 2.[17] There are about 200,000 primary and secondary diagnoses of PH in the United States every year[18]

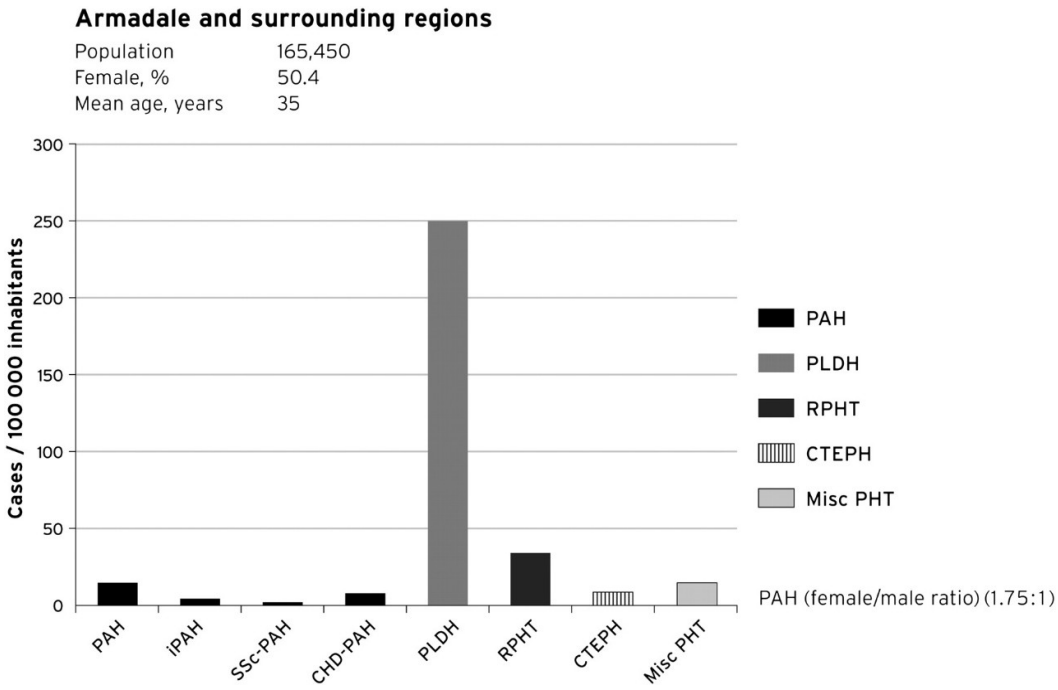
[16] Jiang, Rong; et al. Efficacy and Safety of a Calcium Sensitizer, Levosimendan, in Patients with Right Heart Failure due to Pulmonary Hypertension. September 2017.
[17] Kelly Chin MDMSCS, Richard N. Channick MD, in Murray and Nadel's Textbook of Respiratory Medicine (Sixth Edition), 2016

Exhibit III – PH Sales by WHO Group[19]



Research by Marco Guazzi, MD[20] finds the prevalence of PH-HFpEF is about half the total population of PH using a small population sample. This compares to an Australian study which showed pulmonary hypertension occurring in about 326 cases per 100,000 persons and left heart pulmonary hypertension (WHO Group 2) occuring in about 250 cases per 100,000 persons, the details of which are shown below.[21]

Exhibit IV – Relative Incidence of PH[22]



[18] https://www.thoracic.org/patients/patient-resources/breathing-in-america/resources/chapter-17-pulmonary-hypertension.pdf
[19] Tenax January 2018 Corporate Presentation
[20] Guazzi, M, Pulmonary Hypertension in Heart Failure Preserved Ejection Fraction Prevalence, Pathophysiology, and Clinical Perspectives; Advances in Heart Failure; January 2014.
[21] http://heart.bmj.com/content/early/2012/07/01/heartjnl-2012-301992
[22] Geoff Strange, David Playford, Simon Stewart, Jenny A Deague, Helen Nelson, Aaron Kent, Eli Gabbay. Pulmonary hypertension: prevalence and mortality in the Armadale echocardiography cohort. July 03, 2012. PAH is WHO Group 1; PLHD is pulmonary hypertension secondary to left heart disease, WHO Group 2 and CTEPH is chronic thromboembolic PH, Group 4. http://heart.bmj.com/content/early/2012/07/01/heartjnl-2012-301992

Based on our literature review, there are estimated to be over 3 million heart failure patients with preserved ejection fraction. Roughly half of this group, or from 1.5 million to 2.0 million also have PH and of this subset there are about 500 to 700 thousand with right heart dysfunction. We think, if approved, Levosimendan can penetrate this market by 30% to 40% after several years on the market.

In HFpEF, the development of PH from an increase in left atrial pressure arises from the failure of the heart to fully expand and contract and is seen as a contributor to poor outcomes and increased mortality. This realization highlights the importance of identifying therapeutic interventions for elevated pulmonary pressures. The demand for addressing this most common category of PH has incentivized a search for potential drugs that can achieve the desired outcome. Pulmonary vasodilators, such as oral phosphodiesterase-5 inhibitors, endothelin receptor agonists, soluble guanylate cyclase stimulators and prostacyclins have all been considered as potential treatments for PH HFpEF, however, efficacy has not been established. The consistently poor clincal trial results may indicate that PH-HFpEF patients require a therapy that will provide more than simple pulmonary artery vasodilation. This makes Levosimendan appear to be promising in this problematic disease given the data supporting the drug's ability to provide additional important benefits such as reductions in pulmonary capillary wedge pressure and improvements in right and left ventricular function.

Exhibit V – Group 1 Therapies Not Successful in Group 2

Drug Class	Pulmonary Hypertension WHO Group 1 (PAH)	Pulmonary Hypertension WHO Group 2 (HFpEF)
PDE5 Inhibitors	FDA Approved	Efficacy not established
Endothelin Receptor Antagonists	FDA Approved	Efficacy not established
Soluble Guanylate Cyclase Stimulators	FDA Approved	Efficacy not established
Prostacyclins (IV/SC/Inhaled/Oral)	FDA Approved	Efficacy not established

Trial Design

Tenax is planning to launch a Phase II trial in the third quarter of 2018. Substantial safety work has been performed on Levosimendan, negating the need for another Phase I trial. Tenax is currently preparing an investigational new drug (IND) application with the agency, and announced the results of the pre-IND meeting with the FDA. The agency provided guidance on the proposed Phase II clinical trial for the use of Levosimendan for treatment of PH-HFpEF. The FDA will allow the new Phase II protocol to be submitted under the existing IND and it was supportive of the study design and endpoints.

Based on details provided at a recent conference presentation, we anticipate the study will be a double-blind clinical trial enrolling approximately 50 PH-HFpEF patients in 20 sites, which should last 14 to 18 months. Based on preliminary work, enrollees will have a pulmonary arterial pressure (PAP) equal to or greater than 35, a pulmonary capillary wedge pressure (PCWP) equal to or greater than 20, a cardiac index (CI)[23] of less than or equal to 2.2, a left ventricular ejection fraction (LVEF) of over 40 and be NYHA Class III or IV.

The primary endpoint of the study will be a hemodynamic measure under stress six weeks into treatment seeking a reduction in PCWP and an improvement in CI. Expected secondary endpoints will relate to a change in resting PCWP under a variety of conditions, a change in resting CI, change in pulmonary vascular resistance (PVR) at rest and under stress, a global assessment at week six based on the Likert scale and length of exercise period.

[23] Cardiac Index (CI) is a hemodynamic parameter that relates the cardiac output from left ventricle in one minute to body surface area, thus relating heart performance to the size of the individual. The unit of measurement is liters per minute per square meter (L/min/m2). Source: Wikipedia / https://en.wikipedia.org/wiki/Cardiac_index

Based on management commentary and what has been accomplished in pre-clinical and clinical work to date, infusion for several hours one time per week appears to be the most likely dosing regimen; however, this will be confirmed in Phase II work.

2017 Financial Results

On April 2, 2018, Tenax filed its 2017 form 10-K providing its operating and financial results for the year ending December 31, 2017. The company reported a net loss of ($8.8) million or ($6.27) per share. This compares to a loss of ($43.9) million in 2016 or ($31.24) per share which included a $33.3 million impairment for write down of Levosimendan realted to the development of the drug in LCOS.

Research and development expenses of $3.5 million represented a 73% decline over 2016's $13.1 million. The contraction was predominantly attributable to the conclusion of the LEVO-CTS trial in the early part of the year and the absence of related expenses. Lower salaries and consulting costs also contributed to the decline.

General and administrative expenses of $5.7 million fell 9% over the prior year's level as legal and professional, facility and other costs declined, including lower franchise taxes.

Cash and equivalents of $9.5 million was held on the balance sheet as of December 31, 2017. Cash burn for the year was approximately ($12.1) million, tapering off substantially in the second half. We anticipate cash burn to accelerate throughout 2018 as preparations for a 2H:18 launch of a Phase II trial take place. Tenax management believes that they have sufficient cash to fund operations through 1Q:19.

Reverse Stock Split

Tenax received a notice from the NASDAQ in 2017 notifying the company that they could be at risk of delisting due to the shares trading below $1.00. The notice indicated that they were not in compliance with Nasdaq Listing Rule 5550(a)(2), due to the minimum bid price falling below $1.00 for 30 consecutive days. On February 15, 2018, Tenax proposed an amendment to allow for a reverse stock split to take place prior to year-end 2018. The primary reasons for recommending the reverse split is to maintain NASDAQ compliance and listing on the exchange and to encourage investor interest in the company's shares. After receiving a favorable shareholder vote, a reverse stock split became effective on February 23, 2018 at a ratio of 1:20. On March 12, 2018, the NASDAQ indicated that Tenax had regained compliance with NASDAQ minimum bid price requirements.

Milestones

- Meet with FDA for Phase II Trial Design – 1H:18
- Complete Phase II Design; Begin Trial Enrollment[24] – 2H:18
- Conduct Comprehensive Strategic Alternative Review – 2018
- Raise Capital – 2H:18

[24] Tenax noted in its April 4 press release that it is preparing for a "late June or July start of the trial."

Valuation

We update our model to reflect the new indication in pulmonary hypertension in heart failure with preserved ejection fraction (PH-HFpEF). As discussed above, the potential for this market is large with over 3 million patients with heart failure and preserved ejection fraction. From 50% to 70% of this group also has pulmonary hypertension, resulting in an addressable market of 1.5 to 2.0 million patients.

Our model anticipates that the Phase II trial for PH-HFpEF will be launched in the third quarter with a duration of 18 to 24 months. Following a successful outcome and an end-of-phase-2 meeting with the FDA, we see a longer Phase III trial beginning in 2020, which should last approximately three years. A new drug application submitted to the FDA will follow, and after a one year review period and the anticipated favorable response, we foresee first sales in 2024.

To reflect the uncertainty of trial success, FDA approval and ultimate commercialization, we apply a 15% probability of success and also use a 15% discount rate to reflect broader risks.

We assume approximately 1% penetration of the estimated 1.5 million patients in 2024 to reflect a mid-year launch of the drug and slow initial ramp up as the sales force penetrates the market. We anticipate this will increase over the next five years to reach 15% penetration of the target market. After year six, we anticipate generic competitors and reduce our estimates for price and volume.

Based on our mid-point estimates for Levosimendan vial cost ($750) and the use of four vials per month for an average treatment period of 4.5 months, we project a price of $13,500 per course of treatment. We anticipate 1% drug cost inflation over the duration of exclusivity, and reduce price by 10% per year for the three years following anticipated generic competition.

Development and administrative costs are forecast to be $11 million in 2018, rising steadily to $20 million by 2024, the year Levosimendan is expected to launch. After which costs are forecast to fall dramatically to $9.5 million per year.

While it is not clear which route Tenax will take regarding the commercialization of Levosimendan for PH-HFpEF, our model reflects a partner assuming the commercialization role and paying an all-in (includes amounts for potential upfronts and milestones) 15% royalty on sales to the company. Taxes are anticipated to be 30%[25] after the company works through its NOLs.

We apply a 15% probability of ultimate commercialization based on historical success rates as shown in our frequently cited Clinical Development Success Rates[26] piece. The net result of these assumptions is a target price of $41 per share.

Conclusion

Our original thesis regarding Levosimendan found the drug to be a relatively low risk pursuit given the long-term and broad usage history and support the drug has globally for use in cardiac surgery. However, the trial size and length of time required to conduct a repeat study was deemed to be excessive based on company resources.

As a result, Tenax identified a new indication in PH-HFpEF that is expected to benefit from Levosimendan's mechanism of action and can be pursued with a reasonable cost and time commitment. The indication was also in an area with no other approved treatments. With a body of literature that supports Levosimendan's use in PH-HFpEF, Tenax is meeting with the FDA under the existing IND to identify a successful trial design for the drug. Based on the evidence provided in studies cited and input from medical advisors and the scientific advisory board, we see a strong argument for pursuing this indication. Market size is material and with no other approved therapy available, pricing should be strong and penetration high. Our forecasts are adjusted for historical Phase II trial success rates which generate a target price of $41.00.

[25] The selection of 30% as the all in tax rate takes into account the current 21% federal tax rate and adds state taxes of approximately 5% and an additional amount which reflects the potential for a reversal of the tax rate in the future, and increases in state tax rates to reflect a higher burden for government services being assumed at a local level.

[26] Clinical Development Success Rates 2006-2015. David W. Thomas, Justin Burns, John Audette, Adam Carroll, Corey Dow-Hygelund, Michael Hay.

PROJECTED FINANCIALS

Tenax Therapeutics, Inc. - Income Statement

Tenax Therapeutics, Inc.	2017 A	Q1 E	Q2 E	Q3 E	Q4 E	2018 E	2019 E	2020 E
Total Revenues	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**
YOY Growth	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Cost of goods sold	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Product Gross Margin	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Research and development	$3.5	$1.0	$1.5	$2.0	$2.0	$6.5	$8.8	$9.6
General & administration	$5.7	$1.2	$1.2	$1.2	$1.2	$4.8	$5.2	$5.6
Income from operations	($9.2)	($2.2)	($2.7)	($3.2)	($3.2)	($11.3)	($14.0)	($15.2)
Operating Margin	-	-	-	-	-	-	-	-
Interest Income (expense)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Other expense	($0.4)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Pre-Tax Income	($8.8)	($2.2)	($2.7)	($3.2)	($3.2)	($11.3)	($14.0)	($15.2)
Accrual for Income Taxes	$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	**($8.8)**	**($2.2)**	**($2.7)**	**($3.2)**	**($3.2)**	**($11.3)**	**($14.0)**	**($15.2)**
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**($6.27)**	**($1.55)**	**($1.89)**	**($2.24)**	**($2.23)**	**($7.92)**	**($9.56)**	**($9.87)**
YOY Growth	*1650%*	*-33%*	*-10%*	*156%*	*128%*	*26%*	*21%*	*3%*
Basic Shares Outstanding	1.41	1.42	1.43	1.43	1.44	1.43	1.47	1.54

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

HISTORICAL STOCK PRICE

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