

Dronabinol for the Treatment of Obstructive Sleep Apnea and Ampakines for Treating Central Sleep Apnea, Drug-Induced Respiratory Depression and other breathing diseases are Offering Hope for Patients where There Are No Approved Drugs



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CEOCFO: Dr. Manuso, the first thing you see on your website is RespireRx Pharmaceuticals Inc, formerly Cortex Pharmaceuticals, Inc. Why the change?

Dr. Manuso: Cortex was founded in the late eighties as a company primarily interested in the CNS space to develop ampakines for a variety of neuropsychiatric diseases such as schizophrenia, depression and ADHD. Over the years it

developed ever better versions of the original ampakines, given that not all ampakines are equal. By the time Cortex developed third generation molecules that were less toxic and appeared to be more efficacious, it was too late for them to get financing. Control of the company was taken over by a new management team led by Arnold Lippa and Jeff Margolis and which later included myself. We changed the name to RespireRx to highlight our new focus on developing a portfolio of medicines for the treatment of breathing disorders for which there are no approved medicines – obstructive sleep apnea (OSA), central sleep apnea (CSA), opioid-induced respiratory depression and breathing challenges due to genetic diseases and spinal cord injury. We have been developing the portfolio accordingly. In order to expand our portfolio beyond the ampakines, we acquired Pier Pharmaceuticals, which was developing dronabinol for OSA. The combined entity resulted in a company with over \$150 million of paid in capital and a full suite of Phase 2 clinical stage medicines. Today, RespireRx is a Phase 3-ready company with an extensive portfolio of three ampakines and one cannabinoid focused exclusively on breathing disorders.

“RespireRx is a Phase 3-ready pharmaceutical company with a portfolio of clinical-stage medicines being developed for breathing disorders and respiratory deficits for which there are no approved medicines worldwide – Obstructive Sleep Apnea, Central Sleep Apnea, Opioid-Induced Respiratory Depression and breathing challenges due to genetic diseases and spinal cord injury.” - James S. Manuso PhD

CEOCFO: RespireRX is a biopharmaceutical company focused on the discovery and development of novel drug therapies for the treatment of sleep apnea, drug-induced respiratory depression and other brain-mediated breathing disorders. Why the focus on these breathing disorders? Is there a common thread between them? Is there a common thread in the drugs that you are developing?

Dr. Manuso: The development of neuro-psychiatric drugs by Cortex and others has been particularly difficult because of the subjective nature of the diseases being studied. The primary endpoints used in our clinical trials, such as respiratory

rate and oxygenation, are objective, physiological measurements, unlike the subjective, paper and pencil tests used in psychiatry.

The RespireRx portfolio of medicines consists of dronabinol, which is Phase 3 ready, and three ampakines, two of which are in Phase 2. All are small molecule pills that are focused on the treatment of breathing disorders for which no approved pharmaceuticals exist. Unlike other approaches, these drugs target central and peripheral nervous system sites that modulate breathing and are being developed for disorders such as obstructive and central sleep apnea, as well as the respiratory depression observed in spinal cord injury and Pompe Disorder.

The cannabinoid, dronabinol is a small molecule pill that targets peripheral nervous system sites in order to treat OSA, which is caused by the collapse of the smooth muscles in the throat leading to the prevention of breathing during sleep. Dronabinol decreases the relaxation of these muscles so that normal breathing can be resumed during sleep. OSA is a national health problem with approximately 30 million afflicted Americans -- they stop breathing every night anywhere from five to fifty times an hour. That's NOT snoring.

By contrast, the ampakines targets certain cells in the brain that contain AMPA-type glutamate receptors and regulate respiratory drive. The ampakines act by enhancing the actions of glutamate, the brain's major excitatory neurotransmitter, on its AMPA-type receptors. These same brain cells also contain opioid receptors, which when activated by drugs such as narcotics, depress breathing. In preclinical and clinical studies, the ampakines have demonstrated the ability to overcome the respiratory depressant effects of the opioids without altering their analgesic properties.

Approximately 40 – 50% of patients suffering from Central Sleep Apnea (CSA) are taking opioids for pain management and this CSA is a reflection of opioid induced respiratory depression. Of major importance is the fact that opioid induced respiratory depression is the primary risk factor for opioid overdose and mortality.

In addition, because the ampakines act on those brain cells that modulate breathing, they have potential utility in breathing disorders unrelated to opioid use. For example, published animal studies by our colleagues at the University of Alberta and the University of Florida have demonstrated the ability of ampakines to improve breathing in animal models of spinal cord injury and Pompe Disease.

CEOCFO: *You have two platforms Ampakines and Cannabinoids? Where did these platforms come from and what makes them useful in treating breathing and sleep disorders?*

Dr. Manuso: Dronabinol or delta-9 THC, an active ingredient of marijuana, is a generic cannabinoid drug presently approved by the FDA for the treatment AIDS related cachexia and nausea produced by cancer chemotherapy. Our repurposing approach derives from the research of Dr. David Carley of the University of Illinois Chicago, who demonstrated in preclinical studies that dronabinol improved breathing in an animal model of OSA. RespireRx has licensed exclusive rights from the University of Illinois Chicago to patents claiming the use of cannabinoids for the method of treating sleep-related breathing disorders as well as data obtained in the Phase 2B PACE clinical study conducted by Dr. Carley and his colleagues. This study, as well as a previous Phase 2A clinical study conducted by the Company, demonstrated dronabinol was safe and well tolerated and produced a statistically significant improvement in OSA, when compared to placebo controls. It will serve as the basis for discussions with FDA during 2017 to determine the next steps on the road to an approval for dronabinol in the treatment of OSA.

OSA is defined as a cessation or slowing of breathing for ten seconds or more and for up to 50 times per hour during sleep. The person who has this disease wakes up often because they stop breathing. This is not snoring. It is due to the collapse of the smooth muscles in the throat. There are different levels of severity of OSA, from mild to moderate to severe, depending on the number of times per night breathing is compromised. OSA is now of epidemic proportions in the US, with estimates of approximately 30 million sufferers.

The poor night time sleep produced by OSA can cause excessive daytime sleepiness, thereby predisposing sufferers to a vast variety of accidents. It also can be lethal in conjunction with co-morbidities such as heart failure, stroke and diabetes, where the necessity of blood oxygenation is critical to survival. Let me direct your attention to a couple of recent events regarding excessive daytime sleepiness. The New York Metropolitan Transit Authority has advised that they are going to start examining employees particularly trained engineers with regard to sleep apnea. You may recall on the Hudson line that an engineer literally fell asleep at the switch. The train was derailed and eleven people were killed and others were injured. It was determined that he suffered from OSA and this points out the fact that one of the primary issues with OSA is sleeplessness. If you do not sleep well at night, what can happen during the day is you can nod off. If you suffer from

diabetes or heart disease, if you are an engineer on a train or if you are driving a car or if you are operating heavy equipment, the net result of OSA is a major cost in lives and economics. It is estimated that the annual cost to society of OSA is at \$162 billion.

The primary treatment for patients diagnosed with OSA is the use of devices that produce continuous positive airway pressure or CPAP. While the CPAP devices are very effective, because of their bulkiness and discomfort, less than half of the diagnosed patients use them on a regular basis. Many do not even initiate treatment. Given the large number of patients diagnosed with OSA and the poor compliance with CPAP devices, a significant, unmet medical need exists for a well accepted and easy to take pharmaceutical medication in those patients unable or unwilling to use CPAP.

The ampakines were discovered and developed by scientists at RespireRx. However, the use of ampakines for the treatment of respiratory disorders stemmed from the elegant translational research conducted by Dr. John Greer and his colleagues at the University of Alberta and is the subject of patents claiming the use of ampakines as a method of treating a large number of breathing disorders and which have been exclusively licensed to RespireRx. In three Phase 2A clinical trials, two of the ampakines under development have demonstrated the ability to reduce the respiratory depression produced by fentanyl, a potent opioid. These positive studies have demonstrated target site engagement and proof of principle. The ampakines, currently formulated as small molecule pills, are being developed to treat opioid induced respiratory depression and the CSA it produces, as well as spinal cord injury and certain genetic diseases where breathing is compromised.

With regard to opioids, according to the National Institute of Drug Abuse, we are in the midst of very dangerous opioid epidemic. The danger originates from the respiratory depression produced by the opioids, which is the primary cause of opioid overdose and lethality. The major problem stems from the fact that, while higher opioid doses are required to produce respiratory depression than analgesia, the chronic use of opioids produces tolerance to the analgesia but not the respiratory depression. As a result, higher and higher doses are required to produce the needed pain relief, but that now reach the levels that produce the undesired respiratory depression. While directly acting opioid antagonists, such as Narcan or naloxone, presently are being used as rescue medication to prevent lethality due to overdose, these drugs also reverse the desired opioid analgesia in patients using opioids for pain management. What is needed is a novel pharmacological treatment, like the ampakines, that reduces opioid induced respiratory depression without affecting opioid analgesia.

From a clinical perspective, the appearance of CSA in patients chronically taking opioids is an early and sensitive indicator that the opioid doses have reached the levels that produce respiratory depression. Based on our successful Phase 2A studies and dependent on additional financing, we intend to conduct a Phase 2 study investigating the ability of one or more ampakines to reduce the CSA in a group of patients chronically taking opioids. In addition, RespireRx is considering the development of a combination formulation of an opioid and an ampakine.

As I mentioned earlier, animal studies have demonstrated the ability of ampakines to improve breathing in animal models of spinal cord injury and Pompe Disease and we are considering initiating, in 2017, a Phase 2 clinical trial in patients with spinal cord injury.

CEOCFO: *Will your medications replace or work in conjunction with devices currently on the market when looking for a valid treatment for sleep apnea?*

Dr. Manuso: The answer to this question depends on which drug platform we are discussing. With regard to dronabinol and its use for the treatment of OSA, we don't anticipate dronabinol either competing with or replacing CPAP device, the primary treatment for OSA. As I said earlier, while CPAP is a very effective treatment, the majority of diagnosed patients either don't initiate treatment or don't comply with the prescribed usage. For this reason, oral dronabinol represents a solution for the large, unmet clinical needs of those diagnosed patients who are unable or unwilling to use CPAP. In addition, if an easy to take medicine were available for OSA treatment, we believe that large numbers of the estimated 24 million undiagnosed patients would now come in for diagnosis and treatment.

With regard to the ampakines as a treatment for CSA, there is no approved treatment to replace or with which to be used in conjunction.

CEOCFO: *In December 2016, you announced positive results from Phase 2B PACE (Pharmacotherapy of Apnea by Cannabimimetic Enhancement) Study conducted by the University of Illinois. Dronabinol Reduces Symptoms of Obstructive Sleep Apnea. Would you tell us about those results and where we go from here?*

Dr. Manuso: Our most advanced medicine is dronabinol, which was the drug treatment under evaluation in the recently completed Phase 2B PACE clinical trial for the treatment of OSA. The trial was independently conducted at four medical

centers under the leadership of the University of Illinois Chicago and Northwestern University. It was fully funded by a \$5 million NIH grant.

Of the fifty-six evaluable patients with moderate to severe OSA who completed the study, seventeen received a placebo pill, nineteen received 2.5 milligrams of dronabinol and twenty patients received 10 milligrams of dronabinol, nightly, before “lights out.” In a dose dependent fashion, dronabinol significantly improved the primary outcome measures of Apnea Hypopnea Index (“AHI”), which measures how often a patients stops or reduces breathing, daytime sleepiness as measured by the Epworth Sleepiness Scale (“ESS”) and overall patient satisfaction as measured by the Treatment Satisfaction Questionnaire for Medications (“TSQM”).

These results suggest that, finally, there may be an approvable medicine for select OSA patients.

The results from the PACE trial sets up the circumstances for us meet with FDA later this year to plan out the next and possibly final steps for developing dronabinol through to NDA approval. As I mentioned earlier, dronabinol already is an approved medicine for weight-loss in AIDS patients and nausea and vomiting in cancer patients. As a result, it has a fifteen-year history of safety. On the regulatory front, RespireRx will seek 505b2 designation (to express a new use for an existing medicine) and fast track and breakthrough status for dronabinol in OSA. If the FDA ultimately approves dronabinol for OSA patients, especially for patients who are not being treated by devices at this time, there is a potential to save lives.

CEOCFO: Are you doing presentations to the medical community to explain the value of the therapies you are developing and if so, what has been the response?

Dr. Manuso: We plan to present our data at a number of scientific conferences and will provide details in the future. Furthermore, we typically present our company and our data at a number of investment banking conferences and at select industry-sponsored conferences. For example, on February 13, 2017, at 1:00 PM ET, I will present the RespireRx story at the industry-sponsored BIO CEO & Investor Conference at the Waldorf Astoria Hotel in New York. I will review as much detail as possible in less than a half an hour. I will discuss the portfolio of our medicines, the clinical data, and our business and financing strategies. Most important, investors need to know that dronabinol is Phase III ready and two of the ampakines are Phase II B ready. As investors learn more about RespireRx, the positive response in our stock price has been evident.

The BIO CEO & Investor presentation will be available by live webcast at 1:00 PM on Monday, February 13, 2017. It can be accessed by clicking on the investors tab on the Company’s web-site (www.respirerx.com), and following the links and instructions in a press release announcing this presentation or by going to:

<http://www.veracast.com/webcasts/bio/ceoinvestor2017/36118482417.cfm>.

CEOCFO: RespireRX is currently traded on the OTCQB (call letters RSPI). Are you currently looking to attract investors, participating in conferences and going to road shows? Do you have the funding to continue development and clinical trials? Are you looking for partnerships?

Dr. Manuso: Biotech and pharma companies are always looking for funding and we are no different. At present we are seeking additional financing to take us into the commencement of the continued development of dronabinol and the ampakines. Furthermore, given the expense and labor intensive nature of undertaking and executing a large Phase III trial we will consider a joint venture or other form of partnering for the development of dronabinol. Moreover, there is more to our story than dronabinol, alone. We also will consider alternatives for financing and joint-venturing to develop the ampakines.

CEOCFO: What is your take on the new President Trump administration and the affect their policies may have on drug development?

Dr. Manuso: While I am very hopeful, it is still too early to predict. We all have heard some of the proposals from the White House and members of Congress, but specifics regarding the nature of any changes and the path to implementation need to be better defined. In the case of RespireRx, we are on the cusp of the journey from clinical and regulatory development to an approval, so we are eager to see how all of this plays out.

CEOCFO: In closing, please address our readers in the business, investment and medical communities. Why is RespireRX and your focus important?

Dr. Manuso: First and foremost, RespireRx is the most advanced company worldwide developing oral small molecule medications for truly unmet medical needs in the breathing or respiratory field. We have the potential for tremendous

growth going forward. The RespireRx team has founded, built, grown and sold multiple companies and medicines in the past, for billions of dollars. We have a history of getting medicines approved by the FDA and other international agencies. Realistically, to succeed in the biotech and pharma industries, all you need for success is one medicine that works. We think we have more than one. We have one medicine that is very far along in its journey to becoming the first in the world to be approved for patients suffering from OSA.

Bio: James S. Manuso, Ph.D., MBA

Dr. James S. Manuso is a biotechnology/pharmaceutical industry CEO and entrepreneur experienced in the foundation, management, financing, governance and sale of start-up, public, private, domestic and international companies with marketed and R&D-stage products. He has extensive investment banking, M&A, general management, and business, financial, corporate, and drug development expertise. Dr. Manuso has served as board chairman, and chairman of audit, governance and nominating, pricing and compensation committees of multiple companies' boards. He has executed financings and deals for biotech and pharmaceutical companies in excess of \$1 billion dollars and is considered a "financial expert" under Sarbanes-Oxley regulations.

Dr. Manuso is President, CEO and Vice Chairman of RespireRx Pharmaceuticals Inc. (OTC QB: RSPI), a clinical-stage pharmaceutical company with a Phase 3-ready medicine and three Phase 2 medicines in development, all targeting respiratory diseases for which there are no approved pharmaceuticals. He is Chairman and CEO of Talfinium Investments, Inc., an investment entity and financial consultancy. Immediately prior to this latter appointment, he was a Senior Advisor to Otsuka Pharmaceuticals' executive management. Dr. Manuso served as chairman and chief executive officer of Astex Pharmaceuticals, Inc. (NASDAQ:ASTX), formerly SuperGen (NASDAQ:SUPG), from July 2011 until October, 2013, at which time he sold the company to Otsuka Pharmaceuticals for \$886MM. Previously, from January 2004 to July 2011, he served as chairman, president and CEO, and as a director since February 2001. Dr. Manuso is co-founder and immediate past president and chief executive officer of Galenica Pharmaceuticals, Inc. He co-founded and was general partner of PrimeTech Partners, a biotechnology venture management partnership, from 1998 to 2002, and Managing General Partner of The Channel Group LLC, an international life sciences corporate advisory firm. Dr. Manuso was also president of Manuso, Alexander & Associates, Inc., management consultants and financial advisors to pharmaceutical and biotechnology companies. Earlier in his career, he was vice president and Director of Health Care Planning and Development for The Equitable Companies (now Group Axia), where he also served as Acting Medical Director.

Dr. Manuso served on the boards of The Biotechnology Industry Organization (BIO) and its Health Section Governing Board, Novelos Therapeutics, Inc. (NVL:OB; now Cellectar), Merrion Pharmaceuticals Ltd. (MERR:IEX; Dublin, Ireland), Inflazyme Pharmaceuticals, Inc. (IZP-TSE; Vancouver, Canada), Symbionics, Inc., (sold to BioMarin as ZyStor, Inc. for \$110 Million), Montigen Pharmaceuticals, Inc., Quark Pharmaceuticals, Inc., Galenica Pharmaceuticals, Inc., Supratek Pharma, Inc., EuroGen, Ltd. (London, UK), where he was chairman, and the Greater San Francisco Bay Area Leukemia & Lymphoma Society where he also served as vice president.

Dr. Manuso was educated in France, Greece and the United States. He earned a B.A. with Honors in Economics and Chemistry from New York University, a Ph.D. in Experimental Psychophysiology and Genetics from the Graduate Faculty of The New School University where he was a New School Scholar, a Certificate in Health Systems Management from Harvard Business School, and an Executive MBA from Columbia Business School where he was an Equitable Companies Scholar. Dr. Manuso is the author of over 30 chapters, articles and books on topics including health care cost containment and biotechnology company management. He has taught and lectured at Columbia, New York University, Georgetown, Polytechnic University, and Waseda University (Japan), and he served as a biotechnology consultant to the prime minister of New Zealand. Dr. Manuso has delivered invited addresses at meetings of the American Management Association, the American Medical Association, the Securities Industry Association, the Biotechnology Industry Organization, and many other professional associations.

