RespireRx Pharmaceuticals Inc.
Form 10-K
April 16, 2019

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

[X] Annual Report pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

For the fiscal year ended December 31, 2018

OR

[ ] Transition Report pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

Commission file number 1-16467

RespireRx Pharmaceuticals Inc.

(Exact name of registrant as specified in its charter)

Delaware	**33-0303583**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification Number)**

126 Valley Road, Suite C

Glen Rock, New Jersey 07452

(Address of principal executive offices, including zip code)

(201) 444-4947

(Registrant's telephone number, including area code)

Securities registered under Section 12(b) of the Act: None

Securities registered under Section 12(g) of the Act:

Common Stock, $0.001 par value

(Title of Class)

Indicate by check mark whether the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. YES [ ] NO [X]

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Exchange Act. YES [ ] NO [X]

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act during the preceding 12 months (or for such shorter period that the registrant was required to file such reports); and (2) has been subject to such filing requirements for the past 90 days. YES [X] NO [ ]

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). YES [X] NO [ ]

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405 of this chapter) is not contained herein, and will not be contained, to the best of the registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form

10-K. [ ]

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of “large accelerated filer,” “accelerated filer,” “smaller reporting company,” and “emerging growth company” in Rule 12b-2 of the Exchange Act.

Large accelerated filer	Accelerated filer	Non-accelerated filer	Smaller reporting company	Emerging growth company
[ ]	[ ]	[ ]	[X]	[ ]

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. [ ]

Indicate by check mark whether the registrant is a shell company (as defined in Exchange Act Rule 12b-2). YES [ ] NO [X]

The aggregate market value of the voting stock held by non-affiliates as of June 29, 2018 was approximately $3,164,690 (based on the closing sale price of the common stock as reported by the OTC QB) on June 29, 2018.

As of April 11, 2019, there were 3,872,076 shares of the registrant’s common stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE: NONE

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In this Annual Report on Form 10-K, the terms “RespireRx,” the “Company,” “we,” “us” and “our” refer to RespireRx Pharmaceuticals Inc. (f/k/a Cortex Pharmaceuticals, Inc.), a Delaware corporation, and, unless the context indicates otherwise, its consolidated subsidiaries.

INTRODUCTORY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K of RespireRx Pharmaceuticals Inc. (“RespireRx” or the “Company”) contains certain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934 (the “Exchange Act”) and the Company intends that such forward-looking statements be subject to the safe harbor created thereby. These might include statements regarding the Company’s future plans, targets, estimates, assumptions, financial position, business strategy and other plans and objectives for future operations, and assumptions and predictions about research and development efforts, including, but not limited to, preclinical and clinical research design, execution, timing, costs and results, future product demand, supply, manufacturing, costs, marketing and pricing factors.

In some cases, forward-looking statements may be identified by words including “anticipates,” “believes,” “intends,” “estimates,” “expects,” “plans,” “contemplates,” “targets,” “continues,” “budgets,” “may,” and similar expressions and such sta may include, but are not limited to, statements regarding (i) future research plans, expenditures and results, (ii) potential collaborative arrangements, (iii) the potential utility of the Company’s proposed products, (iv) reorganization plans, and (v) the need for, and availability of, additional financing.

The forward-looking statements included herein are based on current expectations that involve a number of risks and uncertainties. These forward-looking statements are based on assumptions regarding the Company’s business and technology, which involve judgments with respect to, among other things, future scientific, economic, regulatory and competitive conditions, collaborations with third parties, and future business decisions, all of which are difficult or impossible to predict accurately and many of which are beyond the Company’s control. Although the Company believes that the assumptions underlying the forward-looking statements are reasonable, actual results may differ materially from those set forth in the forward-looking statements. In light of the significant uncertainties inherent in the forward-looking information included herein, the inclusion of such information should not be regarded as a representation by the Company or any other person that the Company’s objectives or plans will be achieved.

Factors that could cause or contribute to such differences include, but are not limited to, regulatory policies or changes thereto, available cash, research and development results, competition from other similar businesses, interest of third parties in collaborations with us, and market and general economic factors.

For more information about the risks and uncertainties the Company faces, see “Item 1A. Risk Factors” of this Annual Report on Form 10-K. Forward-looking statements speak only as of the date they are made. The Company does not undertake and specifically declines any obligation to update any forward-looking statements or to publicly announce the results of any revisions to any statements to reflect new information or future events or developments.

PART I

Item 1. Business

The Company's mission is to develop innovative and revolutionary treatments to combat diseases caused by disruption of neuronal signaling. We are developing treatment options that address conditions that affect millions of people, but for which there are few or poor treatment options, including obstructive sleep apnea ("OSA"), attention deficit hyperactivity disorder ("ADHD") and recovery from spinal cord injury ("SCI"), as well as certain neurological orphan diseases such as Fragile X Syndrome. RespireRx is developing a pipeline of new drug products based on our broad patent portfolios for two drug platforms: ampakines, proprietary compounds that positively modulate AMPA-type glutamate receptors to promote neuronal function and cannabinoids, including dronabinol ("Δ9-THC").

Ampakines

Since its formation in 1987, RespireRx Pharmaceuticals Inc. (formerly known as Cortex Pharmaceuticals, Inc.) has been engaged in the research and clinical development of a class of proprietary compounds known as ampakines, a term used to designate their actions as positive allosteric modulators of the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid ("AMPA") glutamate receptor. Ampakines are small molecule compounds that enhance the excitatory actions of the neurotransmitter glutamate at the AMPA receptor complex, which mediates most excitatory transmission in the central nervous system ("CNS"). These drugs do not have agonistic or antagonistic properties but instead positively modulate the receptor rate constants for transmitter binding, channel opening, and desensitization. We currently are developing two lead clinical compounds, CX717 and CX1739, and one pre-clinical compound, CX1942. These compounds belong to a new class of ampakines that do not display the electrophysiological and biochemical effects that lead to undesirable side effects, namely convulsive activities, previously reported in animal models of earlier generations.

The Company owns patents and patent applications, or the rights thereto, for certain families of chemical compounds, including ampakines, which claim the chemical structures, their actions as ampakines and their use in the treatment of various disorders. Patents claiming a family of chemical structures, including CX1739 and CX1942, as well as their use in the treatment of various disorders extend through at least 2028. Additional patent applications claiming the use of ampakines in the treatment of certain neurological and neuropsychiatric disorders, such as Attention Deficit Hyperactivity Disorder ("ADHD") have been or are expected to be filed in the near future.

In 2007, we determined that expansion of our strategic development into the areas of central respiratory dysfunction, including drug-induced respiratory dysfunction, represented cost-effective opportunities for potentially rapid development and commercialization of RespireRx's compounds. On May 8, 2007, RespireRx entered into a license

agreement, as subsequently amended, with the University of Alberta granting RespireRx exclusive rights to method of treatment patents held by the University of Alberta claiming the use of ampakines for the treatment of various respiratory disorders. These patents, along with RespireRx's own patents claiming chemical structures, comprise RespireRx's principal intellectual property supporting RespireRx's research and clinical development program in the use of ampakines for the treatment of central and drug-induced respiratory disorders.

On May 18, 2018, the Company received a letter from counsel claiming to represent TEC Edmonton and The Governors of the University of Alberta that purported to terminate, effective December 12, 2017, the license agreement dated May 9, 2007 (as subsequently amended) between the Company and The Governors of the University of Alberta. The Company, through its counsel, disputed any grounds for termination and notified the representative that it invoked Section 13 of that license agreement, which mandates a meeting to be attended by individuals with decision-making authority to attempt in good faith to negotiate a resolution to the dispute. In February 2019, the Company and TEC Edmonton tentatively agreed to terms acceptable to all parties to establish a new license agreement and the form of a new license agreement. However, the parties have not signed the draft new license agreement pending the Company's payment of the agreed amount of historical unreimbursed patent fees of approximately CAD$23,000 (approximately US$17,000 as of December 31, 2018). No assurance can be provided that the Company will or will not be able to remit the historical license fees or that the draft new license agreement will be executed and become effective. If we do not remit the historical fees and the new license agreement does not become effective, we cannot estimate the possible adverse impact on the Company's operations or business prospects.

Through an extensive translational research effort from the cellular level through Phase 2 clinical trials, the Company has developed a family of novel, low impact ampakines, including CX717, CX1739 and CX1942 that have clinical application in the treatment of neurobehavioral disorders, CNS-driven respiratory disorders, spinal cord injury, neurological diseases, and orphan indications. We have been addressing CNS-driven respiratory disorders that affect millions of people, but for which there are few treatment options and limited drug therapies, including opioid induced respiratory disorders, such as apnea (transient cessation of breathing) or hypopnea (transient reduction in breathing). When these symptoms become severe, as in opioid overdose, they are the primary cause of opioid lethality.

RespireRx has completed pre-clinical studies indicating that several of its ampakines, including CX717, CX1739 and CX1942, were efficacious in treating drug induced respiratory depression caused by opioids or certain anesthetics without altering the analgesic effects of the opioids or the anesthetic effects of the anesthetics. The results of our preclinical research studies have been replicated in three separate Phase 2A human clinical trials with two ampakines, CX717 and CX1739, confirming the translational mechanism and target site engagement and demonstrating proof of principle that ampakines act as positive allosteric modulators of AMPA receptors in humans and can be used in humans for the prevention of opioid induced apnea. In addition, RespireRx has conducted a Phase 2A clinical study in which patients with sleep apnea were administered CX1739, RespireRx's lead clinical compound. The results suggested that CX1739 might have use as a treatment for central sleep apnea ("CSA") and mixed sleep apnea, but not OSA.

RespireRx is committed to advancing the ampakines through the clinical and regulatory path to approval and commercialization. Until recently, RespireRx has focused on the ampakines' ability to antagonize opioid induced respiratory depression both as a translational tool to verify target engagement, as well as an eventual commercial indication. We believe the loss of over 70,000 lives in our country last year alone demands that new solutions for opioid induced deaths be developed to ensure the public health.

To this end, the Company has conducted preclinical and clinical research with CX1739, CX717 and CX1942 in the prevention, treatment, and management of opioid induced apnea, the primary cause of overdose deaths. In particular, we have conducted several Phase 2 clinical trials demonstrating that both CX717 and CX1739 significantly reduced opioid induced respiratory depression ("OIRD") without altering analgesia. Since one of the primary risk factors for opioid overdose is CSA, it is significant that a Phase 2A clinical study with CX1739 produced data suggesting a possible reduction in central sleep apnea.

As there are neither drugs nor devices approved to treat CSA, Company management believes there is the potential for a rapid path to commercialization. Unfortunately, rather than support novel approaches for opioid treatment, the recent public and governmental discourses regarding the "opioid epidemic" has focused almost entirely on the distribution of naloxone, an opioid antagonist used for acute emergency situations, so-called "non-abuseable" opioid formulations, as well as on means of reducing opioid consumption by limiting production of opioids and access to legal opioid prescriptions. It remains to be seen whether these approaches will have an impact on the situation. Nevertheless, as a result, we believe that there is an ongoing industry-wide pullback from opioids, as evidenced by a reduction in opioid prescriptions and a major reduction in manufacturing by two of the largest opioid manufactures in the United States.

These factors have made it difficult to raise capital or find strategic partners for the development of ampakines for the treatment of opioid induced respiratory depression and we are assessing whether to continue with this program. In addition, as noted above, we have been notified by the University of Alberta ("TEC Edmonton") that they consider our license agreement to be terminated and we are in discussions with them to determine whether and under what conditions a resolution to the dispute can be achieved. At the present time, we are suspending the development of this program until we reach an understanding with the University of Alberta, the political climate is clarified and we are able to either raise funding or enter into a strategic relationship for this purpose. Nevertheless, the valuable data derived from these translational studies have established antagonism of OIRD as a biomarker for demonstrating proof of principle and target engagement in support of continued ampakine development for other indications.

In addition, the Company is pursuing potentially promising clinical development programs in neuro-behavioral and cognitive disorders, with translational and clinical research programs focused on the use of ampakines for the treatment of ADHD and, together with our academic collaborators, for motor impairment resulting from SCI and for Fragile X Autism.

ADHD is one of the most common neurobehavioral disorders, with 6.1% of American children taking medication for treatment, and ADHD is estimated to affect 7.8% of U.S. children aged 4 to 17, which is approximately 4.5 million children, according to the U.S. Centers for Disease Control and Prevention ("CDC"). The principal characteristics of ADHD are inattention, hyperactivity and impulsivity. ADHD symptoms are known to persist into adulthood. In a study published in *Psychiatry Res in May 2010,* up to 78% of children affected by this disorder showed at least one of the major symptoms of ADHD when followed up 10 years later. According to the CDC, approximately 4% of the US adult population has ADHD, which can negatively impair many aspects of daily life, including home, school, work and interpersonal relationships.

Currently available treatments for ADHD include amphetamine-type stimulants and non-stimulant agents targeting the monoaminergic receptor systems in the brain. However, these receptors are not restricted to the brain and are widely found throughout the body. Thus, while these agents can be effective in ameliorating ADHD symptoms, they also can produce adverse cardiovascular effects, such as increased heart rate and blood pressure. Existing treatments also affect eating habits and can reduce weight gain and growth in children and have been associated with suicidal ideation in adolescents and adults. In addition, approved stimulant treatments are DEA classified as controlled substances and present logistical issues for distribution and protection from diversion. Approved non-stimulant treatments, such as atomoxetine, can take four to eight weeks to become effective and undesirable side effects have been observed.

Various investigators have generated data supporting the concept that alterations in AMPA receptor function might underlie the production of some of the symptoms of ADHD. In rodent and primate models of cognition, ampakines have been demonstrated to reduce inattention and impulsivity, two of the cardinal symptoms of ADHD. Furthermore, ampakines do not stimulate spontaneous locomotor activity in either mice or rats, unlike the stimulants presently used for the treatment of ADHD, nor do they increase the stimulation produced by amphetamine or cocaine. These preclinical considerations prompted us to conduct a randomized, double-blind, placebo controlled, two period crossover study to assess the efficacy and safety of CX717 in adults with ADHD.

In a repeated measures analysis, a statistically significant treatment effect on ADHD Rating Scale (ADHD-RS), the primary outcome measure, was observed after a three-week administration of CX717, 800 mg BID. Differences between this dose of CX717 and placebo were seen as early as week one of treatment and continued throughout the remainder of the study. The low dose of CX717, 200 mg BID, did not differ from placebo. In general, results from both the ADHD-RS hyperactivity and inattentiveness subscales, which were secondary efficacy variables, paralleled the results of the total score. CX717 was considered safe and well tolerated.

Based on these clinical results, ampakines such as CX717 might represent a breakthrough opportunity to develop a non-stimulating therapeutic for ADHD with the rapidity of onset normally seen with stimulants. Subject to raising sufficient financing (of which no assurance can be provided), we are planning to continue this program with a Phase 2B clinical trial in patients with adult ADHD.

Ampakines also may have potential utility in the treatment and management of SCI to enhance motor functions and improve the quality of life for SCI patients. An estimated 17,000 new cases of SCI occur each year in the United States, most a result of automobile accidents. Currently, there are roughly 282,000 people living with spinal cord injuries, which often produce impaired motor function.

SCI can profoundly impair neural plasticity leading to significant morbidity and mortality in human accident victims. Plasticity is a fundamental property of the nervous system that enables continuous alteration of neural pathways and synapses in response to experience or injury. One frequently studied model of plasticity is long-term facilitation of motor nerve output ("LTF"). A large body of literature exists regarding the ability of ampakines to stimulate neural plasticity, possibly due to an enhanced synthesis and secretion of various growth factors.

Recently, studies of acute intermittent hypoxia ("AIH") in patients with SCI demonstrate that neural plasticity can be induced to improve motor function. This LTF is based on physiological mechanisms associated with the ability of spinal circuitry to learn how to adjust spinal and brainstem synaptic strength following repeated hypoxic bouts. Because AIH induces spinal plasticity, the potential exists to harness repetitive AIH as a means of inducing functional recovery of motor function following SCI.

RespireRx has been working with Dr. David Fuller, at the University of Florida with funding from the National Institutes of Health, to evaluate the use of ampakines for the treatment of compromised motor function in SCI. Using mice that have received spinal hemisections, CX717 was observed to increase motor nerve activity bilaterally. The effect on the hemisected side was greater than that measured on the intact side, with the recovery approximating that seen on the intact side prior to administration of ampakine. In addition, CX717 was observed to produce a dramatic and long-lasting effect on LTF produced by AIH. The doses of ampakines active in SCI were comparable to those demonstrating antagonism of OIRD, indicating target engagement of the AMPA receptors.

These animal models of motor nerve function following SCI support proof of concept for a new treatment paradigm using ampakines to improve motor functions in patients with SCI. With additional funding recently granted by NIH to Dr. Fuller, RespireRx is continuing its collaborative preclinical research with Dr. Fuller while it is planning a clinical trial program focused on developing ampakines for the restoration of certain motor functions in patients with SCI. The Company is working with our Clinical Advisory Panel and with researchers at highly regarded clinical sites to finalize a Phase 2 clinical trial protocol. Subject to raising sufficient financing (of which no assurance can be provided), we believe that a clinical study could be initiated as early as 2019.

According to the Autism Society, more than 3.5 million Americans live with an Autism Spectrum Disorder (“ASD”), a complex neurodevelopmental disorder. Fragile X Syndrome (“FXS”) is the most common identifiable single-gene cause of autism, affecting approximately 1.4 in every 10,000 males and 0.9 in every 10,000 females, according to the CDC. Individuals with FXS and ASD exhibit a range of abnormal behaviors comprising hyperactivity and attention problems, executive function deficits, hyper-reactivity to stimuli, anxiety and mood instability. Also, according the Autism Society, the prevalence rate of ASD has risen from 1 in 150 children in 2000 to 1 in 68 children in 2010, with current estimates indicating a significant rise in ASD diagnosis to 1 in 59 births, placing a significant emotional and economic burden on families and educational systems. The Autism Society estimates the economic cost to U.S. citizens of autism services to be between $236 and $262 billion annually.

Since “autistic disturbances” were first identified in children in 1943, extensive research efforts have attempted to identify the genetic, molecular, environmental, and clinical causes of ASD, but until recently the underlying etiology of the disorder remained elusive. Today, there are no medications that can treat ASD or its core symptoms, and only two anti-psychotic drugs, aripiprazole and risperidone, are approved by the United States Food and Drug Administration (“FDA”) for the treatment of irritability associated with ASD.

Thanks to wide ranging translational research efforts, FXS and ASD are currently recognized as disorders of the synapse with alterations in different forms of synaptic communication and neuronal network connectivity. Focusing on the proteins and subunits of the AMPA receptor complex, autism researchers at the University of San Diego (“UCSD”) have proposed that AMPA receptor malfunction and disrupted glutamate signal transmission may play an etiologic role in the behavioral, emotional and neurocognitive phenotypes that remain the standard for ASD diagnosis. For example, Stargazin, also known as CACNG2 (Ca^{2+} channel 2 subunit), is one of four closely related proteins recently categorized as transmembrane AMPA receptor regulating proteins (“TARPs”).

Researchers at the UCSD have been studying genetic mutations in the AMPA receptor complex that lead to cognitive and functional deficiencies along the autism spectrum. They work with patients and their families to conduct detailed genetic analyses in order to better understand the underlying mechanisms of autism. In one case, they have been working with a teenage patient who has an autism diagnosis, with a phenotype that is characterized by subtle Tourette-like behaviors, extreme aggression, and verbal and physical outbursts with disordered thought. Despite the behaviors, his language is normal. Using next generation sequencing and genome editing technologies, the researchers identified a specific mutation in stargazin, a transmembrane AMPA receptor regulatory protein that alters the configuration and kinetics of the AMPA receptor. When the aberrant sequence was introduced into C57bL6 mice using CRISPR (Clustered Regulatory Interspaced Short Palindromic Repeats), the heterozygous allele had a dominant negative effect on the trafficking of post-synaptic AMPA receptors and produced behaviors consistent with a glutamatergic deficit and similar to what has been observed in the teenage patient.

With funding from the National Institutes of Health to UCSD, RespireRx is working with UCSD to explore the use of ampakines for the amelioration of the cognitive and other deficits associated with AMPA receptor gene mutations. Because CX1739 has an open investigational new drug (“IND”) application, subject to securing sufficient outside funding (of which no assurance can be provided), we are considering a Phase 2A clinical trial sometime in 2019.

Cannabinoids

OSA is a sleep-related breathing disorder that afflicts an estimated 29 million people in the United States according to the American Academy of Sleep Medicine ("AASM"), and an additional 26 million in Germany and 8 million in the United Kingdom, as presented at the European Respiratory Society's ("ERS") annual Congress in Paris, France in September 2018. OSA involves a decrease or complete halt in airflow despite an ongoing effort to breathe during sleep. When the muscles relax during sleep, soft tissue in the back of the throat collapses and obstructs the upper airway. OSA remains significantly under-recognized, as only 20% of cases in the United States according to the AASM and 20% of cases globally have been properly diagnosed. About 24 percent of adult men and 9 percent of adult women have the breathing symptoms of OSA with or without daytime sleepiness. OSA significantly impacts the lives of sufferers who do not get enough sleep; their quality of sleep is deteriorated such that daily function is compromised and limited. OSA is associated with decreased quality of life, significant functional impairment, and increased risk of road traffic accidents, especially in professions like transportation and shipping.

Research has established links between OSA and several important co-morbidities, including hypertension, type II diabetes, obesity, stroke, congestive heart failure, coronary artery disease, cardiac arrhythmias, and even early mortality. The consequences of undiagnosed and untreated OSA are medically serious and economically costly. According to the AASM, the estimated economic burden of OSA in the United States is approximately $162 billion annually. We believe that a new drug therapy that is effective in reducing the medical and economic burden of OSA would have significant advantages for optimal pricing in this costly disease indication.

Continuous Positive Airway Pressure ("CPAP") is the most common treatment for OSA. CPAP devices work by blowing pressurized air into the nose (or mouth and nose), which keeps the pharyngeal airway open. CPAP is not curative, and patients must use the mask whenever they sleep. Reduction of the apnea/hypopnea index ("AHI") is the standard objective measure of therapeutic response in OSA. Apnea is the cessation of breathing for 10 seconds or more and hyponea is a reduction in breathing. AHI is the sum of apnea and hypopnea events per hour. In the sleep laboratory, CPAP is highly effective at reducing the AHI. However, the device is cumbersome and difficult for many patients to tolerate. Most studies describe that 25-50% of patients refuse to initiate or completely discontinue CPAP use within the first several months and that most patients who continue to use the device do so only intermittently.

Oral devices may be an option for patients who cannot tolerate CPAP. Several dental devices are available including the Mandibular Advancement Device ("MAD") and the Tongue Retaining Device ("TRD"). The MAD is the most widely used dental device for sleep apnea and is similar in appearance to a sports mouth guard. It forces the lower jaw forward and down slightly which keeps the airway more open. The TRD is a splint that holds the tongue in place to keep the airway as open as possible. Like CPAP, oral devices are not curative for patients with OSA. The cost of these devices tends to be high and side effects associated with them include night time pain, dry lips, tooth discomfort, and excessive salivation.

Patients with clinically significant OSA who cannot be treated adequately with CPAP or oral devices can elect to undergo surgery. The most common surgery is uvulopalatopharyngoplasty which involves the removal of excess tissue in the throat to make the airway wider. Other possible surgeries include tracheostomies, rebuilding of the lower jaw, and nose surgery. Patients who undergo surgery for the treatment of OSA risk complications, including infection, changes in voice frequency, and impaired sense of smell. Surgery is often unsuccessful and, at present, no method exists to reliably predict therapeutic outcome from these forms of OSA surgery.

Recently, another surgical option has become available based on upper airway stimulation. It is a combination of an implantable nerve stimulator and an external remote controlled by the patient. The hypoglossal nerve is a motor nerve that controls the tongue. The implanted device stimulates the nerve with every attempted breath, regardless of whether such stimulation is needed for that breath, to increase muscle tone to prevent the tongue and other soft tissues from collapsing. The surgically implanted device is turned on at night and off in the morning by the patient with the remote.

The poor tolerance and long-term adherence to CPAP, as well as the limitations of mechanical devices and surgery, make discovery of therapeutic alternatives clinically relevant and important. RespireRx's translational research results demonstrate that dronabinol, a synthetic cannabinoid, has the potential to become the first drug treatment for this large and underserved market.

In order to expand RespireRx's respiratory disorders program and develop cannabinoids for the treatment of OSA, RespireRx acquired 100% of the issued and outstanding equity securities of Pier Pharmaceuticals, Inc. ("Pier") effective August 10, 2012 pursuant to an Agreement and Plan of Merger. Pier had been formed in June 2007 (under the name SteadySleep Rx Co.) as a clinical stage pharmaceutical company to develop a pharmacologic treatment for OSA and had been engaged in research and clinical development activities.

Through the merger, RespireRx gained access to an Exclusive License Agreement (as amended, the "Old License Agreement") that Pier had entered into with the University of Illinois Chicago (the "UIC") on October 10, 2007. The Old License Agreement covered certain patents and patent applications in the United States and other countries claiming the use of certain compounds referred to as cannabinoids, of which dronabinol is a specific example, for the treatment of sleep-related breathing disorders (including sleep apnea). Pier's business plan was to determine whether dronabinol would significantly improve subjective and objective clinical measures in patients with OSA.

The Old License Agreement was terminated effective March 21, 2013 and the Company entered into a new license agreement (the "2014 License Agreement") with the UIC on June 27, 2014, the material terms of which were substantially similar to the Old License Agreement. The 2014 License Agreement grants the Company, among other provisions, exclusive rights: (i) to practice certain patents in the United States, Germany and the United Kingdom, as defined in the 2014 License Agreement, that are held by the UIC; (ii) to identify, develop, make, have made, import, export, lease, sell, have sold or offer for sale any related licensed products; and (iii) to grant sub-licenses of the rights granted in the 2014 License Agreement, subject to the provisions of the 2014 License Agreement. The Company is required under the 2014 License Agreement, among other terms and conditions, to pay the UIC a license fee, royalties, patent costs and certain milestone payments.

Dronabinol is a synthetic derivative of Δ9-THC, one of the pharmacologically active substances naturally occurring in the cannabis plant. Dronabinol is a Schedule III, controlled generic drug that has been approved by the FDA for the treatment of AIDS-related anorexia and chemotherapy-induced nausea and vomiting. Dronabinol is available in the United States as the branded prescription drug product Marinol® capsules. Marinol®, together with numerous generic formulations, is available in 2.5, 5, and 10 mg capsules, with a maximum labelled dosage of 20 mg/day for the AIDS indication, or 15 mg/m^2 per dose for chemotherapy-induced nausea and vomiting.

The Company conducted a 21 day, randomized, double-blind, placebo-controlled, dose escalation Phase 2A clinical study in 22 patients with OSA, in which dronabinol produced a statistically significant reduction in AHI, the primary therapeutic end-point, and was observed to be safe and well tolerated, with the frequency of side effects no different from placebo (Prasad *et al, Frontiers in Psychiatry*, 2013).

With approximately $5 million in funding from the National Heart, Lung and Blood Institute of National Institutes of Health ("NIH"), Dr. David Carley of UIC, along with his colleagues at UIC and Northwestern University, recently completed a Phase 2B multi-center, double-blind, placebo-controlled clinical trial of dronabinol in patients with OSA.

Entitled Pharmacotherapy of Apnea with Cannabimimetic Enhancement (“PACE”), this study replicated the earlier Phase 2A study. The authors reported (Carley *et al*, *Sleep*, 2018) that, in a dose dependent fashion, treatment with 2.5mg and 10mg of dronabinol once a day at night, significantly reduced, compared to placebo, the AHI during sleep in 56 evaluable patients with moderate to severe OSA who completed the study. Additionally, treatment with 10mg of dronabinol significantly improved daytime sleepiness as measured by the Epworth Sleepiness Scale and achieved the greatest overall patient satisfaction. As in the previous study, dronabinol was observed to be safe and well tolerated, with the frequency of side effects no different from placebo. The Company did not manage or fund this clinical trial which was funded by the National Heart, Lung and Blood Institute of NIH.

The use of dronabinol for the treatment of OSA is a novel indication for an already approved drug and, as such, the Company believes that it would allow us or a development partner to submit a 505(b)(2) New Drug Application ("NDA") to the FDA for approval of a new dronabinol label, as opposed to the submission and approval of a full 505(b)(1) NDA. The 505(b)(2) NDA was created by the Hatch-Waxman Amendments to the Federal Food, Drug and Cosmetic Act, in part, to help avoid unnecessary duplication of studies already performed on a previously approved drug; the section gives the FDA express permission to rely on data not developed by the NDA applicant. A 505(b)(2) NDA contains full safety and effectiveness reports but allows at least some of the information required for NDA approval, such as safety and efficacy information on the active ingredient, to come from studies not conducted by or for the applicant. This can result in a less expensive and faster route to approval, compared with a traditional development path, such as 505(b)(1), while creating new, differentiated products. This regulatory path offers market protections under Hatch-Waxman provisions for market exclusivity at the FDA. Other regulatory routes are available to pursue proprietary formulations of dronabinol that will provide further market protections. In Europe, a regulatory approval route similar to the 505(b)(2) pathway is the hybrid procedure based on Article 10 of Directive 2001/83/EC.

In conjunction with its management and consultants, RespireRx has developed a regulatory strategy in which we intend to file a new NDA under Section 505(b)(2) claiming the efficacy of dronabinol in the treatment of OSA and, in the process, create a new branded product. We have engaged Camargo Pharmaceutical Services, LLC to act as regulatory consultants and assist with FDA filings and regulatory strategy.

Unlike a standard 505(b)(1) NDA, the 505(b)(2) Abbreviated New Drug Application ("ANDA") process begins with a pre-IND meeting with the FDA, then moves to formulation development (and nonclinical studies, if necessary) and then to the IND (investigational new drug) filing. Since we intend to utilize an already approved or equivalent dronabinol product from manufacturers that have approved Drug Master Files, we believe that the pre-IND meeting will forego discussions of CMC (chemistry, manufacturing and controls), formulation and safety, as well as Phase 1 and 2 studies. Instead, we believe that the focus will be on the Phase 3 clinical development program. When a Phase 3 study is required for a 505(b)(2), usually only one study with fewer patients is necessary versus the two, large scale, confirmatory studies generally required for 505(b)(1). While no assurance can be provided, with an extensive safety database tracking chronic, long-term use of Marinol® and generics, we believe that FDA should not have major safety concerns with dronabinol in the treatment of OSA.

We anticipate requesting a pre-IND meeting with the FDA possibly during the second quarter of 2019, which would functionally serve as the equivalent of an end-of-Phase 2 meeting. The FDA responses to this meeting will be incorporated into an IND, which we believe we could be in a position to submit within 60 days of receiving their communication.

RespireRx has worked with the PACE investigators and staff, as well as with our Clinical Advisory Panel to design a Phase 3 protocol that, based on the experience and results from the Phase 2A and Phase 2B trials, we believe will provide sufficient data for FDA approval of a RespireRx dronabinol branded capsule for OSA. Subject to raising sufficient financing (of which no assurance can be provided). RespireRx intends to submit the Phase 3 protocol to the FDA. The current version of the protocol is designed as a 90-day randomized, blinded, placebo controlled study of

dronabinol in the treatment of OSA. Depending on feedback from the FDA, RespireRx estimates that the Phase 3 trial would require between 120 and 300 patients at 15 to 20 sites, and take 18 to 24 months to complete, at a cost of between $10 million and $14 million.

Subject to raising sufficient financing (of which no assurance can be provided), RespireRx intends to hire Clinilabs Drug Development Corporation, a full-service CRO, to consult and potentially provide clinical site management, monitoring, data management, and centralized sleep monitoring services for the Phase 3 OSA trial. Dr. Gary Zammitt, CEO of Clinilabs, serves on the RespireRx Clinical Advisory Panel, and his management team has provided guidance on study design and CNS drug development that will be relevant for the Phase 3 program. For example, Clinilabs offers specialized clinical trial services for CNS drug development through an alliance with Neuroclinics, including clinical trials examining the effects of drugs on driving, cognitive effects of food and (medicinal) drugs, and sleep and sleep disordered breathing.

On September 4, 2018, RespireRx entered into a dronabinol Development and Supply Agreement with Noramco Inc., one of the world's major dronabinol manufacturers. Under the terms of the Agreement, Noramco agreed to (i) provide all of the active pharmaceutical ingredient ("API") estimated to be needed for the clinical development process for both the first- and second-generation products (each a "Product" and collectively, the "Products"), three validation batches for NDA filing(s) and adequate supply for the initial inventory stocking for the wholesale and retail channels, subject to certain limitations, (ii) maintain or file valid drug master files ("DMFs") with the FDA or any other regulatory authority and provide the Company with access or a right of reference letter entitling the Company to make continuing reference to the DMFs during the term of the agreement in connection with any regulatory filings made with the FDA by the Company, (iii) participate on a development committee, and (iv) make available its regulatory consultants, collaborate with any regulatory consulting firms engaged by the Company and participate in all FDA or Drug Enforcement Agency ("DEA") meetings as appropriate and as related to the API.