



**Dronabinol for Obstructive Sleep Apnea Syndrome  
Executive Summary**

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## RespireRx Overview

The mission of RespireRx Pharmaceuticals is to develop innovative and revolutionary treatments to combat respiratory diseases caused by disruption of neuronal signaling. We are addressing respiratory conditions that affect millions of people, but for which there are few treatment options and no drug therapies, including obstructive sleep apnea (OSA), central sleep apnea (CSA), and disordered breathing from spinal cord injury (SCI) and neural dysfunction. Additionally, we are developing new drugs and formulations that address the widespread problem of opioid overdose, which results from opioid-induced respiratory depression (OIRD), both in patients who are on chronic opioid therapy for pain management and in the post-surgical setting.

RespireRx is developing a pipeline of new drug products based on our broad patent portfolios for two drug platforms, including dronabinol ( $\Delta$ -9THC), and the ampakines, which positively modulate AMPA-type glutamate receptors to promote neuronal function.

This executive summary provides an overview of the dronabinol platform for the treatment of OSA, including market opportunity, regulatory path, and financial projections.

### **Strategic Focus: Dronabinol for the Treatment of Obstructive Sleep Apnea**

RespireRx holds the exclusive world-wide license to a broad family of patents for the use of cannabinoids in the treatment of sleep related breathing disorders from the University of Illinois at Chicago (UIC). There are six issued patents, and we have several extensions and pending applications that will extend patent protection for over a decade.

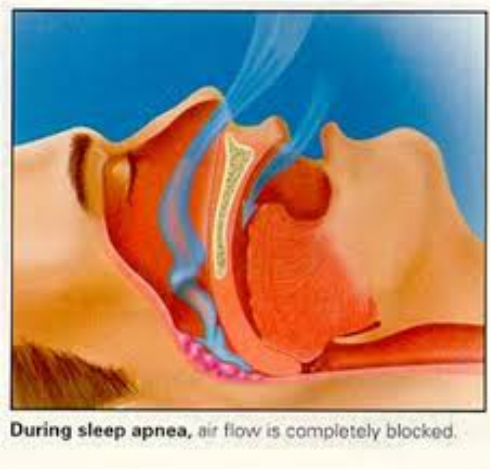
The inventor, Dr. David Carley at UIC, recently completed a Phase 2B multi-center, double-blind, placebo-controlled clinical trial of dronabinol in patients with OSA replicating the earlier Phase 2A clinical trial results, that demonstrated statistically significant improvements in respiration, daytime sleepiness, and patient satisfaction with therapy. This clinical trial was fully funded by a ~\$5 million grant from the National Heart, Lung and Blood Institute of the National Institutes of Health, and the results were presented at the annual meeting of the 31st Annual Meeting of the Associated Sleep Professional Societies LLC in June 2017, and described below.

Under the terms of the license agreement, RespireRx now holds the exclusive rights to develop and commercialize dronabinol for sleep related breathing disorders. The use of dronabinol for the treatment of OSA is a new indication for an already approved drug, thereby allowing RespireRx or a development partner to submit a 505(b)2 application to FDA for approval of a new dronabinol label. This regulatory path may offer market protections under Hatch-Waxman provisions for market exclusivity at FDA. Other regulatory routes are available to pursue proprietary formulations of dronabinol that will provide further market protections.

## Meeting the Challenge of Obstructive Sleep Apnea

Obstructive sleep apnea syndrome (OSA) is a sleep-related breathing disorder that afflicts an estimated 29 million people in the United States and over 100 million people worldwide. 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 21% in the U.S. and 20% globally have been properly diagnosed. About 24 percent of adult men and nine 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 (QOL), 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. For example, epidemiologic studies from around the world have consistently identified body weight

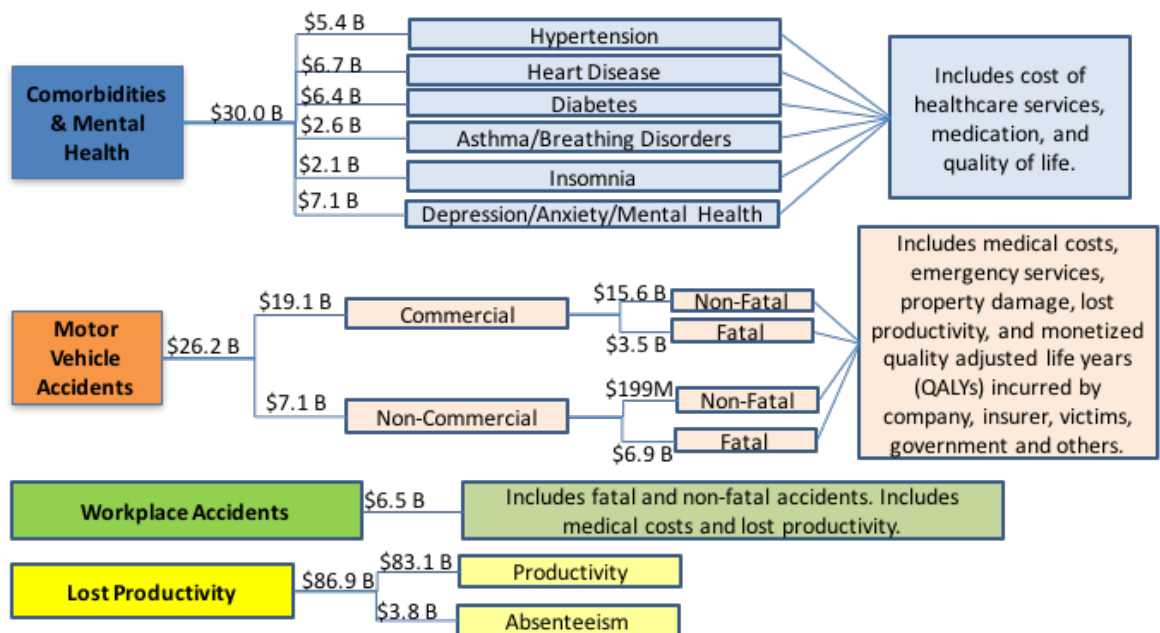


as the strongest risk factor for obstructive sleep apnea, and the Wisconsin Sleep Cohort study showed that a one standard deviation difference in body mass index (BMI) was associated with a 4-fold increase in disease prevalence. Excess body weight is a common clinical finding and is present in more than 60% of the patients referred for a diagnostic sleep evaluation.

Over the last 10 to 15 years, there have been dramatic increases in the number of overweight and obese adults in the United States and this obesity epidemic is believed to have contributed to an explosive growth of OSA and other sleep related disorders.

Furthermore, the consequences of undiagnosed and untreated OSA are medically serious and economically costly. As illustrated in Figure 1, the economic burden of OSA in the U.S. is staggering, with cost estimates ranging to \$162 Billion annually.

**Figure 1. Economic Costs of Obstructive Sleep Apnea**



Source: American Academy of Sleep Medicine - 2016

Interestingly, the costs of undiagnosed OSA far exceed the costs of diagnosis and treatment, as illustrated in Table 1, which shows that the average cost to treat a patient with OSA is approximately \$2,100 per year, but untreated OSA

costs three times as much at \$6,300 per patient. Clearly, a new drug therapy that is effective in reducing the medical and economic burden of OSA will have significant advantages for optimal pricing in this costly disease indication.

Pharmacologic treatment for OSA is essentially non-existent due to the complexity of the neurochemical control and neuromodulation of central respiratory drive and the upper airway motor output. Nevertheless, the poor tolerance and long-term adherence to Continuous Positive Airway Pressure (CPAP) treatment in OSA, make discovery of such therapeutic alternatives clinically relevant and important. RespireRx' translational research results demonstrate that dronabinol has the potential to become the first drug treatment for this large and underserved market.

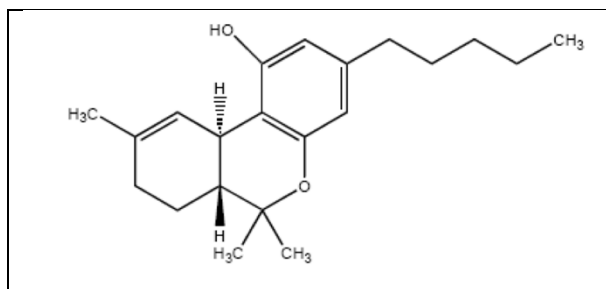
**Table 1. Economic Burden of Obstructive Sleep Apnea:  
Cost Differential in Diagnosed vs. Undiagnosed Patients in the U.S. 2016**

Undiagnosed		Diagnosed	
# People with OSA	23,500,000		5,900,000
	Cost of Undiagnosed OSA (\$US Bil)		Cost of Diagnosed OSA (\$US Bil)
Comorbidities & Mental Health	\$30.0	Diagnosis, Testing and Follow Up	\$0.8
Motor Vehicle Accidents	\$26.2	Non-surgical Treatment	\$6.2
Workplace Accidents	\$6.5	Surgical Treatment	\$5.4
Lost Productivity	\$86.9		
<b>Total Costs (\$US Bil)</b>	<b>\$149.6</b>		<b>\$12.4</b>
Cost per Person	\$6,336		\$2,105

Source: <sup>1</sup>Primary research with experts, secondary clinical research, U.S. Census (2014), Peppard "Increased Prevalence of Sleep-disordered Breathing in Adults." *American Journal of Epidemiology* (2013), Frost & Sullivan Patient Survey, American Academy of Sleep Medicine

### Dronabinol

Dronabinol is a Schedule III, controlled generic drug that has been approved by the U.S. FDA for the treatment of AIDS-related anorexia and chemotherapy-induced emesis. 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<sup>2</sup> per dose for chemotherapy-induced emesis.



Dronabinol is synthetic delta-9-tetrahydrocannabinol ( $\Delta^9$ -THC)

**Chemical Name:** (6aR-trans)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

## **Current Therapy & Unmet Medical Need**

Continuous Positive Airway Pressure (CPAP) is the most common treatment for OSA. CPAP devices work by blowing pressurized air into the 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. 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 use the device 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 former 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 adequately treated with CPAP or oral devices can elect to undergo surgery. The most common surgery is uvulopalatopharyngoplasty (UPPP), 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 any form 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.

Given the limited efficacy of most of the surgical options and the associated risks and the poor long-term compliance for mechanical devices, there exists a significant unmet medical need for a safe and effective treatment for OSA. A drug for the treatment for OSA has been sought for many years, but effective agents remain to be identified. Discovery efforts have been hampered by an incomplete understanding of the basic pathological mechanisms leading to apnea, lack of appropriate animal models to develop and test treatment strategies, and the multi-factorial nature of OSA.

## **Translational Research in OSA**

Through an extensive series of translational research projects from the cellular level through proof-of-concept clinical trials, research has demonstrated that dronabinol is an effective drug therapy for OSA.

### **Pathophysiology of OSA and Therapeutic Rationale for Development of Dronabinol**

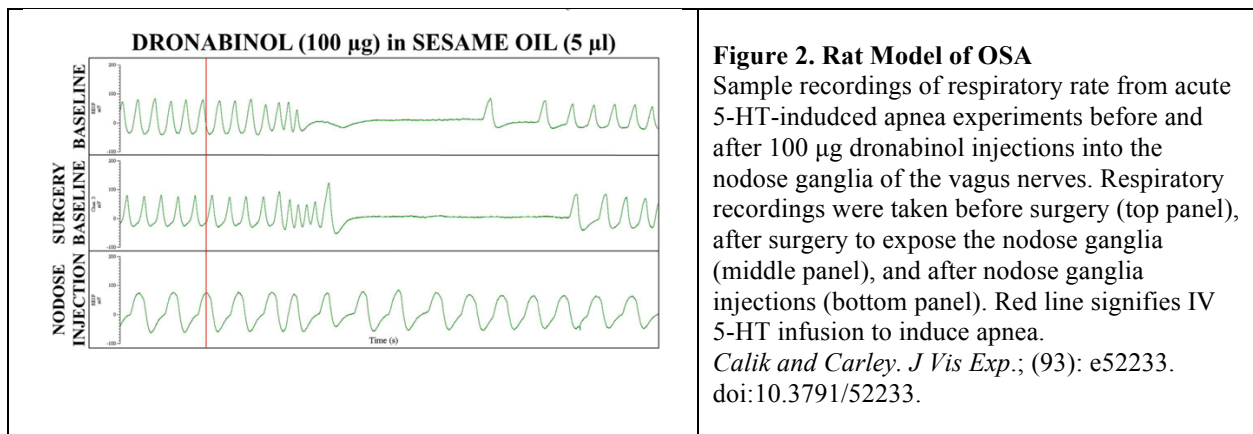
The pathogenic mechanisms leading to OSA have not been fully defined despite several decades of intensive investigation. Four factors affecting upper airway patency have been identified: 1) redundant oro- and hypopharyngeal tissue, 2) edema within these same tissues, 3) narrow airway caliber, and 4) increased airway collapsibility. During wakefulness, these stressors are successfully counterbalanced by activation of intrinsic dilating muscles within upper airway structures. With sleep onset, the relevant neuromuscular compensatory reflexes become at least intermittently inadequate, leading to upper airway obstruction in the form of apnea (transient cessation of airflow) or hypopnea (transient reduction in airflow). Apneas and hypopneas, in turn, produce

hypoventilation with hypoxia and hypercapnia as well as concomitant increases of inspiratory effort, culminating in arousal from sleep and restoration of airflow. This cycle can repeat hundreds of times in a single night of sleep. While no true standard exists, it is generally accepted that AHI ranges of 5-15, 15-30, and >30 reflect mild, moderate, and severe OSA, respectively.

The American Academy of Sleep Medicine (AASM) recognizes that sleep related breathing disorders arise from a combination of neural dysregulation and an inadequately defended upper airway system. Fenik et al. (2001) showed that pharmacologic modulation of sensory neurons located in the nodose ganglia and innervating the airways may play an important role in regulating both inspiratory effort and in setting the level of activity in the upper airway dilator muscles. On this basis, Dr. David Carley, the inventor of our licensed patents from the University of Illinois-Chicago, hypothesized that vagus afferent neurons based in the nodose ganglia may exert an important influence on the compensatory abilities of a compromised upper airway, and thus on the predisposition of an individual to experience sleep-related apneas and hypopneas. This possibility has therapeutic implications for sleep related breathing disorders, as the excitability of nodose ganglion neurons is regulated by a number of endogenous neurotransmitter systems, including endocannabinoids, serotonin (5HT), GABA, dopamine and opioids.

The pharmacologic rationale for developing dronabinol for the treatment of OSA is based on the role of vagal imbalance in OSA. Dr. Carley and his colleagues created rat models of OSA by measuring spontaneously occurring sleep apneas as well as apneas produced by injections of 5HT, which altered vagal tone through its actions on 5HT receptors in the nodose ganglia. Recognizing that the excitability of nodose ganglion neurons can be regulated by cannabinoids, Dr. Carley and his colleagues conducted a series of translational research experiments to ascertain the ability of cannabinoids to reduce OSA and determine their mechanism and site of action.

As illustrated in Figure 2, these studies demonstrated that dronabinol, acting at CB1 & CB2 receptors in the nodose ganglion, was able to attenuate 5HT-induced reflex apneas in the rat model of OSA.



In a rat model of sleep related breathing disorders, dronabinol injections produced dose-dependent reductions in sleep apneas either spontaneously occurring or induced by 5HT injections, during both NREM and REM sleep (Carley et al. SLEEP, Vol. 25, No. 4, 2002). Acute injections of dronabinol also improved sleep consolidation and deep sleep, and this represents an important potential secondary benefit, as repetitive arousals from sleep are thought to contribute importantly to daytime sleepiness, one of the primary symptoms of OSA.

**Clinical Development of Dronabinol**

**Positive Results of a Phase 2A Study of Dronabinol in OSA**

Based on Dr. Carley’s preclinical results, the Company conducted a 21 day, randomized, double-blind, placebo-controlled, dose escalation Phase 2 clinical study in 22 patients with OSA, in which dronabinol produced statistically significant reductions in the Apnea-Hypopnea Index (AHI), the primary therapeutic end-point, and was

observed to be safe and well tolerated (Prasad *et al*, *Frontiers in Psychiatry*, 2013). Compared to baseline, dronabinol treatment produced a statistically significant improvement in AHI, with an overall reduction of 32%. Both the 2.5 mg and 10 mg doses of dronabinol significantly reduced AHI (events/hr) from baseline (LS (least squares) mean change -10.43 and -13.27; p-values = 0.007 and 0.036, respectively). The AHI reduction produced by the 5 mg dose (LS mean change -5.78), however, did not reach statistical significance (p-value = 0.166). The placebo group, on the other hand, showed an increase of 6.37 events/hr, which was significantly different from the 2.5 mg and 10 mg doses (p = 0.011 and 0.018, respectively) but not significantly different from the intermediate 5 mg dose (p = 0.067), as shown in Table 2.

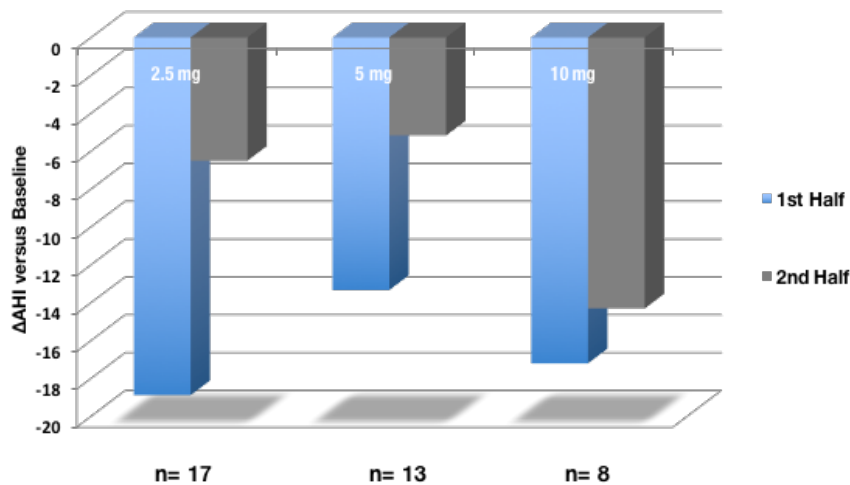
As illustrated in Figure 3, during the first half of the night, the 2.5 mg and 5.0 mg doses of dronabinol were equally effective as the 10 mg dose in reducing AHI. In the second half of the night, however, only the 10 mg dose maintained the effect. Since the blood half-life of dronabinol is ~4 hours, the effectiveness of the lower doses appears to dissipate once drug levels fall below a minimal therapeutic level. Low-dose dronabinol, which is covered by a pending patent, may be therapeutically effective with a controlled release, proprietary formulation.

Quantitative EEG measures of the sleep process in these patients demonstrated that increasing doses of dronabinol were associated with a shift in EEG power toward delta and theta frequencies and a strengthening of ultradian rhythms in the sleep EEG (Carley *et al*, *J. Clinical Sleep Medicine*, 2014). These results suggest that oral dronabinol may improve restorative aspects of the sleep process, contributing to the observed decrease in daytime sleepiness, despite the absence of changes in overall sleep stage percentages or sleep efficiency.

**Table 2. AHI Scores (Events/hr): Absolute Change from Baseline (Efficacy Evaluable Population)**

Parameter	Placebo	Dronabinol		
		2.5 mg	5 mg	10 mg
Patients <sup>1</sup>	4	17	13	8
Observations	12	23	17	8
LS Mean <sup>2</sup>	6.37	-10.43	-5.78	-13.27
p-value <sup>3</sup>	0.198	0.007	0.166	0.036
LS Mean Difference <sup>4</sup>	--	-16.81	-12.16	-19.65
p-value <sup>5</sup>	--	0.011	0.067	0.018

<sup>1</sup> The number of patients receiving the specified dose at the time of the measurement. Patients could receive any dose level for more than one treatment period; therefore, the number of observations may be greater than the number of patients. Computations include all observations at a particular dose.  
<sup>2</sup> LS mean of difference from baseline.  
<sup>3</sup> P-value for the null hypothesis that mean treatment effect (LS Mean) is equal to zero.  
<sup>4</sup> LS mean difference of dronabinol treatment from placebo.  
<sup>5</sup> P-value for the comparison of dronabinol versus placebo at each dose level.



**Figure 3.** Seventeen adults with OSA were administered dronabinol after baseline polysomnogram (PSG), starting at 2.5mg once daily. The dose was increased weekly, as tolerated, to 5mg and finally to 10mg once daily. Repeat PSG assessments were performed on nights 7, 14, and 21 of dronabinol treatment. Change in AHI (DAHI, mean  $\pm$  SD) was significant from baseline to night 21 for the entire night (14.117.5;  $p = 0.007$ ) at the 10 mg dose. The change in AHI at the 2.5 mg and 5.0 mg doses was statistically significant only for the first half of the night.

#### Summary of Phase 2A Efficacy Results:

The efficacy results clearly showed that all three dronabinol doses resulted in a significant improvement (decrease) in AHI scores compared to a worsening of scores in the placebo group. Further, in the supine position, all dronabinol treatments had further improvements in AHI scores compared to placebo. There was no apparent dose dependence to the dronabinol improvements as the 2.5 mg and 10 mg doses had similar decreases relative to placebo overall as well as in the supine position, however, the 5 mg dose improvements were less than the other dronabinol doses. Similar significant improvements were observed with the dronabinol treatments during non-REM sleep; however, the greatest improvements (more than 3 times) were seen in the first half compared to the second half of sleep time. Compared to placebo, the dronabinol doses had no significant improvement on Sleep Efficiency and Arousal Index scores. Duration of arterial oxygen saturation  $<90\%$  and absolute minimum oxygen saturation were not significantly affected by dronabinol. However, the overall mean values for the minimum oxygen saturation were improved  $>2\%$  in the 2.5 and 10 mg dronabinol doses, consistent with the greatest improvement in AHI scores observed with these doses.

#### Summary of Phase 2A Safety Results:

There were no Serious Adverse Events (SAEs) reported during the study. A total of 7 patients reported 8 non-Treatment Emergent Adverse Events (TEAEs) in the study. The incidences of TEAEs are summarized in Table 11 by preferred term (PT) for two or more patients who reported the specific event. For patients with multiples of the same PT, the patient was only counted once. The placebo group reported the greatest overall incidence of any TEAE, while the 5 mg dronabinol treatment had the lowest. Consistent with the Marinol<sup>®</sup> prescribing information, the most frequent TEAEs occurred as nervous system disorders (sedation, somnolence, dizziness and headache); the 2.5 mg dronabinol treatment reporting the highest incidences. Although fewer patients were treated with the 5 and 10 mg dronabinol doses, the incidences decreased considerably in these treatment periods. Most of the TEAE incidences were considered drug-related (possibly, probably or definitely) including those in the placebo group. All TEAEs were either mild or moderate except for one placebo-treated subject who reported a severe headache. There were no reports of adverse changes in physical examination or vital signs. These results support the safety and tolerability of repeated doses of dronabinol.



**Table 3. Incidence ( $\geq 2$  Patients) TEAEs by Preferred Term (Safety Population)**

Parameter	Placebo	Dronabinol		
		2.5 mg	5 mg	10 mg
Treated Patients <sup>1</sup>	5 (100.0%)	17 (100.0%)	14 (100.0%)	8 (100.0%)
Patients with at least one TEAE	4 (80.0%)	13 (76.5%)	8 (57.1%)	6 (75.0%)
Dry Mouth	0	5 (29.4%)	1 (7.1%)	1 (12.5%)
Sedation	0	5 (29.4%)	0	0
Somnolence	1 (20.0%)	5 (29.4%)	2 (14.3%)	4 (50.0%)
Increased Appetite	1 (20.0%)	4 (23.5%)	0	0
Dizziness	1 (20.0%)	4 (23.5%)	1 (7.1%)	0
Fatigue	0	2 (11.8%)	1 (7.1%)	1 (12.5%)
Headache	3 (60.0%)	2 (11.8%)	1 (7.1%)	0

<sup>1</sup> Counts and percentages are based on the number of patients receiving the specified dose for the given period. Patients with multiple AEs within a particular SOC are only counted, and patients with multiples of the same PT are only counted once.

#### Clinical Results Guide Future Reformulation Opportunities

Analysis of the efficacy results by time of night has provided potential guidance on development of new, proprietary formulations of dronabinol. Low dosages of dronabinol, which are covered by a pending patent, may be therapeutically effective with a controlled release, proprietary formulation. Numerous opportunities exist for reformulation of dronabinol to produce a proprietary, branded product for the treatment of sleep disordered breathing. The pharmacokinetic profile of dronabinol is well-known, allowing for reformulations that are within the safety parameters established by commercially available dosage forms. A Phase I study conducted with Marinol outlines the pharmacokinetic measures for daily dronabinol usage (see Table 3).

**Table 4. Summary of Multiple-Dose Pharmacokinetic Parameters of Dronabinol in Healthy Volunteers under Fasted Conditions**

MEAN (SD) PK PARAMETER VALUES			
BID DOSE	C <sub>MAX</sub> NG/ML	MEDIAN T <sub>MAX</sub> (RANGE), HR	AUC (0-12) NG-HR/ML
2.5 mg	1.32 (0.62)	1.00 (0.50-4.00)	2.88 (1.57)
5 mg	2.96 (1.81)	2.50 (0.50-4.00)	6.16 (1.85)
10 mg	7.88 (4.54)	1.50 (0.50-3.50)	15.2 (5.52)

#### Positive Results of a Phase 2B Study of Dronabinol in OSA - The PACE Trial

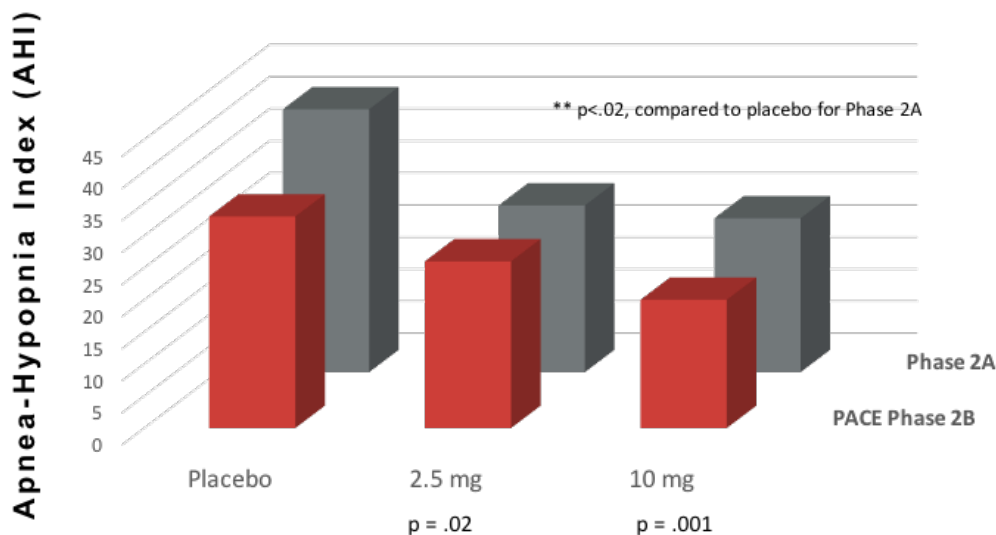
The recently completed PACE (Pharmacotherapy of Apnea by Cannabimimetic Enhancement) trial was a fully-blinded, two-center, Phase II, randomized placebo-controlled trial of dronabinol in 56 adult patients with moderate to severe OSA. By random assignment, 56 adult subjects with BMI<45, Epworth Sleepiness Scale (ESS)>7 and PSG-documented AHI between 15 and 50 received either placebo (N=17), 2.5mg (N=19) or 10.0mg (N=20) of

dronabinol daily, one hour before bedtime for 6 weeks. Repeat in-laboratory PSG followed by maintenance of wakefulness (MWT) testing was completed every 2-weeks during the treatment period. At each visit, the ESS and Treatment Satisfaction Questionnaire for Medications also were completed.

Overall, baseline AHI was  $26.0 \pm 11.6$  (SD) and this was equivalent among all treatment groups. In comparison to placebo, statistically significant end of treatment declines in AHI were observed for both the 2.5 and 10 mg doses ( $-9.7 \pm 4.1$ ,  $p=0.02$  and  $-13.2 \pm 4.0$ ,  $p=0.001$ , respectively). Statistically significant declines in ESS were observed for subjects receiving 10 mg dronabinol ( $-4.0 \pm 0.8$  units,  $p=0.001$ ) but not those receiving 2.5 mg or placebo. Subjects receiving 10 mg dronabinol also expressed the greatest overall satisfaction with treatment ( $p=0.02$ ).

The figure below illustrates how the PACE Trial replicated the statistically significant primary endpoint results of the Phase 2a study.

**Figure 4. PACE Trial Summary: Efficacy in the Treatment of OSA - AHI Scores**



\* Double blind, placebo controlled dose-ascending study in patients with OSA, n=19

Through an extensive series of translational research projects from the cellular level through proof-of-concept clinical trials, research has demonstrated that dronabinol is an effective drug therapy for the widespread and underappreciated disease, OSA.

**Market Exclusivity & Expedited Regulatory Opportunities**

RespireRx hold the exclusive worldwide license to a broad family of patents from the University of Illinois covering the use of dronabinol in the treatment of sleep-related breathing disorders.

Dronabinol also is eligible for market protection under the Hatch-Waxmann Act clause for “other significant changes” (“OSC”) exclusivity period. In addition to patents, the Hatch-Waxman provision may provide significant market protection for a branded generic formulation of dronabinol for three years.

Because there are no approved drug therapies for OSA, dronabinol may be eligible for the FDA’s expedited approval process. There are four programs: fast track, breakthrough therapy, accelerated approval, and priority review. Fast track designation is typically given in the pre-clinical stage, so therefore not applicable to dronabinol. The other three pathways have many similarities and overlapping benefits, as illustrated in the table below. All four programs are designed to address an unmet medical need for a serious condition, defined by FDA as a disease or condition associated with morbidity that has substantial impact on day-to-day functioning.

**Table 5. FDA Expedited Approval Process**

<b>Breakthrough Therapy Designation</b>	Preliminary clinical data	Substantial improvement on clinically significant endpoint(s) over available therapies	<ul style="list-style-type: none"> <li>• More frequent meetings with FDA</li> <li>• More frequent FDA communication</li> <li>• Rolling review</li> <li>• Intensive guidance on an NDA</li> <li>• FDA help to expedite development</li> </ul>
<b>Accelerated Approval Pathway</b>	Not specified; Sponsor should make justification of alternate endpoint based scientific support	Generally provides a meaningful advantage over available therapies <b>AND</b> demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or a clinical endpoint that can be measured earlier than irreversible morbidity or mortality	<ul style="list-style-type: none"> <li>• Approval based on a surrogate or intermediate endpoint (often allows for shorter development time)</li> <li>• Note: FDA requires clinical trials to be conducted post-approval to confirm clinical benefit</li> </ul>
<b>Priority Review Designation</b>	Data contained in the final NDA submission	Significant improvement in safety or effectiveness of the treatment, prevention, or diagnosis of a serious condition	<ul style="list-style-type: none"> <li>• Review of application in 6 months</li> </ul>

**Regulatory & Market Strategies**

**Regulatory steps with dronabinol.** Our interaction with FDA will require a request for a Pre-IND Meeting, because we do not have an open IND. We need to get an IND number, so that we can file the end-of-phase 2 meeting request. With the Pre-IND meeting request, we submit a pre-IND package, and present the phase 2 results to FDA. One possible approach would be to request a NDA under the 505(b)2 regulatory process, relying on the two completed studies.

**Dronabinol is safe.** With an extensive safety database tracking chronic, long-term use of Marinol and generics, FDA should not have a safety issue with dronabinol in the treatment of OSA. Further, dronabinol represents a safe alternative to address the completely unmet medical need for a treatment for obstructive sleep apnea when compared to the broadening use of Sativex (which is not yet approved in the U.S.) and medical marijuana that deliver variable doses of THC in combination with countless unknown substances.

**Multiple development paths for dronabinol.** As part of the strategic analysis of dronabinol development, RespireRx commissioned a regulatory & market assessment by Joseph Martinez, RPh of Commercialization Consulting, LLC. Dronabinol can be developed through the 505(b)2 regulatory process along two different pathways, depending on the goals and capabilities of a strategic development partner. The assessment concludes that the two clinical development strategies for dronabinol, each has advantages and disadvantages.

1. The most direct route to commercialization is to proceed directly to a Phase 3 pivotal trial using the currently available generic formulation (2.5, 5 and 10 mg) of dronabinol and commercialize a “Branded Generic” for the treatment of obstructive sleep apnea. This approach can be implemented simultaneously with the development of a proprietary dronabinol formulation (see below).

**Advantages:**

- 3-year Hatch-Waxman regulatory provision for market exclusivity and protection may be available.
- Formulations currently available from contract manufacturers
- Development costs limited to 1 Phase 3 trial with <300 patients
- Rapid path to market introduction ~ 24 months
- Immediate opportunity to become “The number 1 drug company in the sleep apnea business”
- Establish market and formulary positions with Branded Generic for OSA to protect the brand

**Disadvantages:**

- Generic doses of dronabinol are available on all formularies, and therefore may be inappropriately substituted at the pharmacy
- Physicians will write the generic name with the dose: i.e. dronabinol 10 mg, which will lead to generic substitution
- Reimbursement will be less than 100% of OSA prescriptions written
- Payers will not discourage generic substitution
- Completely generic market following the end of Hatch-Waxman exclusivity period

Using specific market access, education and contracting strategies, Commercialization Consulting estimates that it is possible to protect 85% of the real-world dispensing of dronabinol within 12 months of FDA approval of a Branded Generic Dronabinol for OSA.

The use of a branded generic strategy would include:

- A. Managed markets, government contracting, and supplemental rebates for health plans and hospital systems
    - i. Meetings with medical and pharmacy directors on specific placement for and coding of Branded Dronabinol for OSA
  - B. Providing up-to-date information to pharmacy consulting service companies for healthcare plan payers
    - i. Ensure ECRI Institute and The Hayes Group has full clinical information to provide an accurate and timely monograph to their clients
  - C. Education of:
    - i. Specialist and primary care prescribers to include the diagnosis of OSA on the written or electronic prescription for Branded Dronabinol
    - ii. Pharmacists that Branded Dronabinol is the only FDA-approved product for the treatment of OSA
2. The second strategy is to commercialize a dronabinol formulation that is currently not available as a generic drug. In this scenario, the Phase 3 pivotal trial is delayed until a new proprietary dronabinol product (dose and duration of action) is developed. Optimally, the company will develop two dose levels of dronabinol with differential drug release properties for evaluation in the Phase 3 pivotal trial for the treatment of OSA. With approved doses that are not currently available on the market, the company can eliminate generic competition and substitution. For example, 4 mg and 8 mg controlled release dronabinol formulations have no generic equivalents, so therefore cannot be substituted, even in the absence of a brand name on the prescription.

**Advantages:**

- Long-term market exclusivity with multi-layered patent protection: Use, dose, formulation, delivery
- Minimal generic substitution at point of sale (POS)
- Opportunity to capture and own the market through awareness and marketing campaigns
- Establish multi-level barriers to market entry for generic competitors
- Significantly increased sales over the life of the patents

**Disadvantages:**

- Longer time to market (add 12 to 18 months)
- Additional formulation development costs (~\$500,000)
- Additional manufacturing costs (TBD)
- Additional clinical trial costs for Phase 1 PK studies
- Added development risk for untested strengths and formulations

**Clinical Advisory Panel**

RespireRx has established a clinical advisory panel (CAP) composed of experts in the field of pulmonary health, sleep medicine, and pain management. The board includes physicians and researchers from academia and industry who will advise on the development of dronabinol and advise on the scientific direction of the organization.

**Financial and Budgeting Information**

For FDA approval and commercialization, a Phase 3 trial of dronabinol in OSA will be required. The clinical trial protocol will be written in conjunction with the clinical advisory panel and a licensing partner, however, some estimates of cost and time can be projected for budgeting and planning purposes. To that end, RespireRx estimates that the Phase 3 trial will require less than 300 patients at ~15 sites, and take approximately 24 months to complete, at a cost of roughly \$12 - 14 million.

**Revenue Forecast**

The market potential for a new drug treatment for OSA is enormous, with a target market of nearly 20 million people in the U.S. alone. The original patent for the use of dronabinol for OSA is valid through 2025, so a Branded Generic Dronabinol at 80% of the price of current generic dronabinol products, and with only a maximum 10% market share, still achieves annual revenues exceeding \$11 billion, as illustrated in Table 6.

**Table 6.** Revenue Model for Dronabinol in the Treatment of OSA

Phase III 2017 - 2018, NDA 2019	Year - US Launch 2020	2020	2021	2022	2023	2024	2025
Price/Day*	United States OSAS Population**	19,000,000	19,380,000	19,767,600	20,162,952	20,566,211	20,977,535
\$15	% Share	1%	5%	10%	10%	10%	10%
2% Annual Incidence Increase	# Patients Treated	190,000	969,000	1,976,760	2,016,295	2,056,621	2,097,754
3% Annual Price Increase	Sales	\$ 1,040,250,000	\$ 5,464,433,250	\$ 11,147,443,830	\$ 11,370,392,707	\$ 11,597,800,561	\$ 11,829,756,572
*C-PAP Monthly rental \$250 (\$8.33/day)		**Academy of Sleep Medicine Estimate					

### Special Note Regarding Forward-Looking Statements

*Certain statements included or incorporated by reference in this Executive Summary, including information as to the future financial or operating performance of the Company and its drug development programs, constitute forward-looking statements. The words "believe," "expect," "anticipate," "contemplate," "target," "plan," "intend," "continue," "budget," "estimate," "may," "schedule" and similar expressions identify forward-looking statements. Forward-looking statements include, among other things, statements regarding future plans, targets, estimates and assumptions. Forward-looking statements are necessarily based upon a number of estimates and assumptions that, while considered reasonable by the Company, are inherently subject to significant business, economic and competitive uncertainties and contingencies. Many factors could cause the Company's actual results to differ materially from those expressed or implied in any forward-looking statements made by, or on behalf of, the Company. Due to these various risks and uncertainties, actual events may differ materially from current expectations. Investors are cautioned that forward-looking statements are not guarantees of future performance and, accordingly, investors are cautioned not to put undue reliance on forward-looking statements due to the inherent uncertainty therein. Forward-looking statements are made as of the date of this news release and the Company disclaims any intent or obligation to update publicly such forward-looking statements, whether as a result of new information, future events or results or otherwise.*

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