

**RESPIRATORY
DEVICES**

Sleep Apnea Devices: The Changing Of The Guard

The current, specialty-dominated care paradigm for sleep apnea can't scale up to meet the demands of an enormous and serious chronic disease. New companies aim to remove that bottleneck by moving treatment and diagnosis to the frontline physicians who see patients first.

BY MARY STUART

- Sleep apnea is a large market with room for both new diagnostics and therapies; it's a \$4 billion global market today largely based on a single product area.
- Because sleep apnea is associated with many important core disease areas – cardiovascular disease, obesity, and diabetes – companies have long looked at the condition as a strategic growth opportunity, but they haven't been able to realize the potential value.
- Referral patterns, market fragmentation and the hegemony of clinical and commercial stakeholders – sleep physicians and the respiratory product companies that serve them – have made it difficult for companies with new products to break into this market.
- Recently, innovation in sleep apnea has been accelerating in a new direction, one that breaks the logjams by including not only sleep specialists, but the frontline physicians – primary care docs and cardiologists – who see patients the most.

The 25-year-old field of sleep medicine, now covering some 80 different disorders, is still emerging, and the role of sleep itself remains shrouded in mystery. For the group of diseases categorized as sleep disordered breathing, however, the picture is becoming clearer. There is now widespread recognition that the breathing stoppages resulting from obstructive sleep apnea (OSA) do more than disrupt sleep. OSA has come to be viewed as a co-morbidity, a risk factor, a catalyst, or even a causal agent for many serious diseases.

Sleep apnea in all of its forms (OSA, central sleep apnea and mixes of the two) has strong links to cardiovascular conditions like atherosclerosis, myocardial infarction, hypertension, stroke, and heart failure. It also has a strong association with metabolic disorders, including obesity and diabetes. Whether sleep apnea itself brings on these other diseases or not, it's clear that no good can come

of the intermittent hypoxia, release of stress hormones, and other noxious things that happen all night long when an apneic gasps for breath numerous times per hour.

Obstructive sleep apnea, accounting for the majority of sleep disordered breathing, is essentially a mechanical problem. In certain patients, because of anatomic features (large tonsils, large tongue, excess fat in the neck, flabby tissue, a long soft palate or uvula, or a certain jaw structure) the breathing cycle will result in a narrowing of the upper airway. Specifically, when a person breathes in, he or she creates negative pressure in the upper airway (behind the tongue and soft palate), and in some people that negative pressure causes a collapse of the upper airway, resulting in the vibration that triggers snoring, or even the complete blockage of the airway and an episode of apnea.

With anywhere from 18 to 50 million people in the US with sleep apnea (a consensus on numbers is hard to come by; prevalence is estimated at 9 to 24% of men, and 4 to 9% of women in the 30 to 60 age group), most of it undiagnosed, this is a growth opportunity for medical device companies, and one in a space that is adjacent to many of the major diseases upon which they focus. (See Exhibit 1.) The problem for those who want to break in, however, has always been how to make money in this market, which, although large, has grown up with one dominant therapy and one dominant method of diagnosis targeted to a boutique specialty.

The treatment of obstructive sleep apnea has created a \$4 billion global market dominated by respiratory companies targeting pulmonologists who are sleep physicians with essentially two product areas, continuous positive airway pressure (CPAP) devices and polysomnography (sleep testing monitors).

Respiratory companies such as leaders **ResMed Inc.**, **Respironics Inc.** (a division of **Royal Philips Electronics NV** since 2008), as well as **Fisher Paykel Healthcare Corp. Ltd.** and the **Viasys Healthcare Inc.** division of **Cardinal Health Inc.**, have come to own sleep apnea therapy. Indeed, so tight is the leaders' hold on the space that

not long ago, **Covidien Ltd.** divested its sleep product line, to focus more on the product areas where it has more than a fighting chance.

These companies sell \$2 billion worth of continuous positive airway pressure devices, which have emerged as the gold standard and dominant treatment for OSA. CPAP devices prevent the collapse of the upper airway while a patient sleeps by blowing in air from a piece of durable medical equipment that uses electricity and a face mask. They are prescribed by sleep physicians with the expertise to titrate them properly for individual patients during sleep studies. CPAP is theoretically a universal solution that props open the upper airway regardless of the source of the breathing obstruction, but in practice, lack of compliance with the devices mean that half of the patients for whom CPAP is prescribed stop using their devices within one year because they find them so uncomfortable.

Pulmonologists, board certified in sleep medicine, have historically controlled the diagnostic side of the business. Sleep testing traditionally takes place in sleep laboratories that are usually housed in either hospitals or free-standing centers. Polysomnography, the conventional sleep testing method, measures numerous channels of information from EEG, EKG, EMG, respiratory, movement, and other measurement devices while a patient sleeps overnight in the laboratory, and requires significant expertise for interpretation.

There are treatment alternatives for obstructive sleep apnea; procedures such as uvulopalatopharyngoplasty, which removes tissue in the back of the throat, and maxillomandibular advancement surgeries, which move the upper and lower jaw forward, but few patients choose these invasive surgeries because many feel that the treatment is worse than the disease. Device companies are innovating to develop minimally invasive surgical implants targeted to the ENT market, to stiffen the upper palate (the approach of Restore Medical Inc., for example, which is now part of **Medtronic Inc.**) or to keep the tongue from blocking airflow during sleep. Finally, there are non-invasive oral appliances designed to reposition the tongue and jaw, the province of an emerging specialty called sleep dentistry. However, it has been difficult for companies to grab large markets from these products, for a number of reasons.

First, many of the alternative device therapies work on an assumption concerning the cause of the obstruction, and efficacy is not assured; it can be difficult to predict which patients can benefit from a particular anatomy-repositioning product. Even if a minimally invasive surgical procedure and device that cures sleep apnea can be developed, in the current health care delivery system, treating sleep apnea patients is further hampered by physician referral patterns. There is no clear path that gets patients from the sleep laboratory to the ENT physician or maxillofacial surgeon.

That hasn't stopped Medtronic from creating a surgical business around sleep disordered breathing for its ENT division; in 2008, in addition to its acquisition of Restore Medical and its implant for snoring, Medtronic acquired the *Repose* product line, a bone screw system

for the treatment of obstructive sleep apnea, from **Influent Medical Inc.** (See "Once Sluggish Sleep Apnea Gets Active," START-UP, January 2009.) Medtronic also spun off a neurostimulation approach to obstructive sleep apnea, the basis for venture-backed **Inspire Medical Systems Inc.**, which will compete with neurostimulation companies **Apnex Medical Inc.** and **ImThera Medical Inc.** (See Exhibit 2.) But these new surgical products will need to prove efficacy that is superior to non-invasive products like CPAP and oral appliances (an equation that needs to take into consideration the compliance problems with the latter product categories). Having met that hurdle, new therapies will be further challenged, since under the current diagnostic paradigm, patients see sleep physicians first, and these physicians will tend to wait for patients to balk at or fail CPAP before sending the patient to a second kind of specialist for treatment.

Exhibit 1

The High Prevalence Of Sleep Apnea

DEFINED POPULATION SEGMENT	PREVALENCE OF SLEEP APNEA
People aged 30-60 (US)	9-24% for men, 4-9% for women ¹
Prevalence of moderate to severe OSA (AHI≥15 events per hour)	In the middle-aged population, 11.1% in men and 4.9% in women ²
Obese patients with type 2 diabetes	87% ⁴
Patients with drug-resistant hypertension	83%
Obese patients	77%
Patients with heart failure	76%
Patients with pacemakers	60% with undiagnosed sleep apnea, 21% with severe (AHI≥30 per hour) ³
Patients with atrial fibrillation	49%
Patients with diabetes	48%
All patients with hypertension	37%
Patients with coronary artery disease	30%

¹The Wisconsin Cohort Study; ²The Sleep Heart Health Study; ³Patrick Lévy, MD, PhD, *Circulation* 2007;115:1703–1709; ⁴The SLEEP Ahead Study, lead author Gary Foster, PhD, of the Center of Obesity Research and Education at Temple University.

SOURCE: All statistics are from www.ResMed.com except where otherwise indicated

A SEA CHANGE ON THE HORIZON

Despite the challenges, in recognition of the need for new therapies for obstructive sleep apnea, venture-backed start-ups have been developing alternatives to CPAP, and the large sleep companies have made a few small-dollar acquisitions to broaden their therapeutic offerings, ResMed tucking in Laboratoires Narval SA, paying \$12 million for the manufacturer of a mandibular repositioning device, and Resprionics quietly acquiring venture-backed Aspire Medical Inc., which was running clinical trials on a minimally invasive implant for sleep apnea caused by tongue-based obstruction.

These are incremental movements, however, not likely to change the two giant limitations in the field; first, the fact that perhaps 90% of people with obstructive sleep apnea remain undiagnosed, and sec-

ond, compliance with the gold standard therapy (CPAP) is terrible. Half of all patients drop out of therapy after a year. This has been the story for two decades of sleep apnea care, and it was still the case when *START-UP* spoke to several sleep apnea companies in 2008. (See “Sleep Apnea: A High Growth Device Market Awakens,” *START-UP*, March 2008.)

But in 2010, disruptive change may be occurring in the field of sleep apnea, and it seems to have come on almost overnight. Three new companies are emblematic of a shift – in both diagnostics and treatment – beyond the sleep therapy specialist to some of the front-line physicians who are the first to see patients with sleep apnea: primary care physicians and cardiologists. This shift has two driv-

ers: first, new diagnostic products that don't require the same kind of specialized expertise as CPAP and polysomnography, and second, two key reimbursement decisions by the Centers for Medicare and Medicaid Services (CMS). The changes that are afoot within industry may seem sudden, but they began in March of 2008.

Indeed, when we look back at the development of the field of sleep apnea one day, we will probably find it to have been the product of discontinuous evolution. After a couple of decades of stepwise expansion in one direction, at some point, the evolutionary curve was suddenly disrupted, and it began to rise rapidly in a different direction. That point of disruption occurred in 2008 when the decisions of the CMS brought official recognition to the flaws in the gold

Exhibit 2

Selected Medical Device Start-Ups Targeting Sleep Apnea

COMPANY	PRODUCT DESCRIPTION/VENTURE CAPITAL BACKERS
ADVANCED BRAIN MONITORING	<i>ARES</i> is home sleep testing device that rests on the head like a visor, requiring no lead wires, exclusively licensed to Watermark Medical. <i>Apnea Guard</i> is removable oral/dental appliance for mandibular repositioning
ALAXO	<i>AlaxoStent</i> is reusable (for an estimated six months), removable, self-expandable shape memory metal braid that a patient inserts through the nose and into the throat each night./Private funding.
APNEX	<i>Hypoglossal Nerve Stimulation</i> system is like small pacemaker implanted just below the collarbone, with a wire lead connecting to the hypoglossal nerve. Automatically turns on when a patient is asleep and off during waking hours./Domain Associates, New Enterprise Associates, Polaris Venture Partners, Michael Berman.
CARDIAC CONCEPTS	Addressing central sleep apnea with <i>RespiCardia</i> , a neurostimulation device targeting the phrenic nerve./Affinity Capital, Polaris Venture Partners, Three Arch Partners, Versant Ventures, Accuitive Medical Ventures.
BIANCAMED	Home sleep testing technology offers non-contact system, requires no face mask, no electrodes, bands or patches. BiancaMed has developed algorithms for analyzing the ECG (cardiac) signal to detect sleep apnea; licensed to several companies including SpaceLabs, for its Lifescreen Apnea system. BiancaMed is also developing its own home test, <i>SleepMinder</i> , incorporating RF-based measurement tool to detect patient movement during sleep./Seventure, ePlanet, ResMed, Enterprise Ireland.
CLEVELAND MEDICAL DEVICES	A range of wireless devices with various numbers of channels for performing sleep studies. <i>SleepView</i> , according to company, is smallest and lightest home sleep monitor with AASM recommended Type 3 channel set; interfaces with company's Web portal./Cuyahoga County New Product Development and Entrepreneurship Loan Fund.
DISCOVER MEDICAL DEVICE	<i>SomnuSeal</i> line of intra-oral, self-adaptable face masks to increase the comfort of CPAP.
IMTHERA	<i>Aura6000</i> is neurostimulation system to treated tongue-based obstructions. Two implantable components include rechargeable pulse generator placed in the upper chest, and a self-sizing elastic cuff containing a six-contact electrode, implanted on the hypoglossal nerve. External components include remote control device for controlling and recharging implant. Physician software on a notebook PC permits calibration and titration./Private investors.
INSPIRE MEDICAL	Spun off from Medtronic in 2007; the Inspire II closed-loop system consists of an implantable pulse generator, a pulmonary pressure sensor that senses a patient's respiration during sleep, and a stimulation lead that delivers electrical impulses to the patient's hypoglossal nerve./Kleiner Perkins Caufield & Byers, US Venture Partners, GDN Holdings.
ITAMAR MEDICAL	<i>WatchPat</i> is non-invasive home sleep testing device that uses unique signal, peripheral arterial tonometry./Medtronic, Bay City Capital.
PAVAD MEDICAL	Undisclosed implantable therapy for obstructive sleep apnea./Canaan Partners, MedVenture Associates, Vivo Ventures.
VENTUS MEDICAL	<i>Provent</i> is single-use disposable for creating positive expiratory pressure in patients with obstructive sleep apnea./De Novo Ventures, Johnson & Johnson Development Corp., Mohr Davidow Ventures.
WATERMARK MEDICAL	Home sleep testing system makes use of cloud computing for end-to-end solution that links 135,000 primary care physicians to sleep physicians./CA Technologies, Ballast Point Ventures.

SOURCE: Elsevier's *Strategic Transactions*

standard diagnostics and therapies for sleep apnea, opening the field to new products.

First, the CMS announced that it would cover home sleep testing, hitherto not covered, including alternative testing systems that are often simpler than those offered in sleep laboratories, and in its memorandum issued the strong statement, “PSG [polysomnography] is used as a reference standard in many clinical trials; however, we do not believe it is a true gold standard.”

That decision was important because it opened up a new product market, one that would also help bridge clinical gaps in the field, namely, the underdiagnosis of the disease because of the expense and lack of capacity in the industry. As has often been discussed, patients once had to wait several months for a sleep testing session. The \$2,000 to \$3,000 expense of the studies also meant that diagnosis and therapy decisions for a chronic disease had to rely on a patient trying to sleep for a single night in the strange environment of the sleep laboratory, under surveillance, and tethered to machines and their leads. Results were not likely to reflect what patients experienced in their lives. The home sleep testing coverage was expanded in 2009 to acknowledge numerous types of testing alternatives to PSG, and a new market began to take off.

The acceptance of alternative tests for sleep apnea patients enabled the second decision by CMS; that to be reimbursed, patients for whom CPAP is prescribed have to undergo a 12-week trial period during which physicians (and perhaps more to the point, payors) have the opportunity to assess patient compliance, the biggest hurdle with CPAP. As noted, by one year, 50% of patients have stopped using the therapy, which needs to be used every night for life, and many patients who stick with the devices still don't meet a very low standard for compliance, which is defined as using CPAP for 70% of nights for four hours. CPAP manufacturers have put a lot of effort into trying to improve compliance with devices that self-adjust to patients' airflow, offer air humidification, more comfortable face masks, and lighter-weight units, but these still won't address the fact that a lot of patients simply can't tolerate having something on their faces while they sleep, or the feeling of isolation that comes from being tethered to an air pressure generator that makes noise. The CMS memorandum stated, “The long-held belief that fixed pressure CPAP therapy is the standard is being challenged.”

These changes are good for patients and for industry, and are welcomed by sleep physicians because they create an environment where alternative diagnostics and therapies might improve access to care for the large number of people with sleep apnea currently not receiving sufficient care for a disease that creates long-term health problems.

Philip Westbrook, MD, is a pioneer in sleep medicine, having worked in the field since its beginning. From 1980 to 1989, Westbrook was founding director of the Sleep Disorder Centers at the Mayo Clinic College of Medicine and performed the same role at Cedars-Sinai Medical Center from 1989 to 1995. Westbrook is the

former president of the American Sleep Disorders Association, and is now the chief medical officer of new sleep apnea therapy company **Ventus Medical Inc.**, as well as an inventor of one of the diagnostic devices employed by **Watermark Medical Inc.** “I hope you understand my biases,” Westbrook says. “I am board certified in sleep medicine and have been for years, but I am a great believer that we have wasted a lot of money, time, effort and talent on diagnosing sleep apnea, making it difficult when it's not, and not spending the kinds of resources we should have to treat it.”

Three new companies, at least, believe they can shift this paradigm, with products that enable frontline physicians to become the new gatekeepers in sleep apnea: Watermark Medical and Ventus Medical empowering the primary care physician, and **Cardiac Concepts Inc.** giving heart failure specialists a new therapy to help their patients.

SLEEP TESTING ON A CLOUD

The founders of Watermark Medical came to sleep apnea from a background in cardiology. CEO and co-founder Sean Heyniger was the founder of PDSHeart Inc., an ambulatory arrhythmia monitoring company acquired by **CardioNet Inc.** in 2007, and President Charlie Alvarez was an executive vice president and national sales manager at both arrhythmia monitoring companies. The two brainstormed with John Sculley

(the former CEO of Apple Computer Inc., a board member at PDS-Heart, and now on the board of Watermark Medical) around a new business idea for obstructive sleep apnea, a disease that had always figured prominently in their earlier discussions with cardiologists, since it runs hand in hand with arrhythmias, hypertension, myocardial infarction and heart failure. Ultimately, the trigger for the Watermark business plan was the approval by CMS, noted above, of a CPT code for home sleep testing in March 2008.

“One of our driving principles is that you have to know who is going to pay for what you are offering,” Heyniger notes, a lesson that was no doubt reinforced by his experience at CardioNet, which has been hampered by insufficient reimbursement. (See “*CardioNet: The Promise and Perils of Wireless Medicine*,” IN VIVO, March 2010.) With that question answered for home sleep testing, the team set out to solve the obvious gap in the field of sleep apnea: providing access to care for the 90% of patients with undiagnosed (and therefore untreated) sleep apnea. The key to that access, Watermark's founders believed, would be to reach the frontline physicians who see the target patients the most, the primary care physicians.

To do so, Watermark focused not on developing a new, easy-to-use and reliable diagnostic device; Heyniger acknowledges that many companies are working in that area. These include **Itamar Medical Ltd.**, which has developed *WatchPat*, a device that doesn't require a face mask, belts or electrodes to be placed on the body. Itamar's watch-like device placed on the wrist and cuffs placed on the index and ring fingers are all that's required for the non-invasive diagnosis of sleep apnea with a new biometric called peripheral arterial tonometry (along with measurements of heart rate and oxygen saturation).

“I am a great believer that we have wasted a lot of money, time, effort and talent on diagnosing sleep apnea, making it difficult when it's not, and not spending the kinds of resources we should have to treat it.”
-Philip Westbrook

Venture-backed **BiancaMed Ltd.** is another new company hoping to offer an easy-to-use, patient-friendly device for home sleep testing. (See Exhibit 2.) For its own diagnostic device, Watermark licensed the patient-friendly **ARES (Apnea Risk Evaluation System)** device from **Advanced Brain Monitoring Inc.** The device was originally developed by Philip Westbrook.

Heyniger points out that Watermark's business model is not centered on specific products and services, but rather on providing an end-to-end solution to the diagnosis and treatment of sleep apnea by making use of a cloud-computing platform. "ARES is just one HST [home sleep test] on the market. The heart of our system is the workflow, the platform we have created," he explains. The point, Heyniger says, is "to make it easy not only for the 6,000 sleep physicians, but also for the 135,000 primary care physicians to diagnose and appropriately treat patients with OSA."

The Watermark system begins with a clinically validated screening questionnaire designed to have a high likelihood of identifying patients with OSA before the test. The use of the questionnaire also helps to reassure insurance companies of the cost-effective use of home sleep studies. Because the questionnaire is hosted on the cloud, as are the other information components of this system, "We enable employers or other large groups to push it out to potentially hundreds of thousands of employees, either through the Web or through text SMS [text messaging]," says Heyniger.

After completing the screening, the patient takes home the ARES device, which is like a visor that is worn at bedtime. After a night of sleep testing, the device is returned to the doctor's office, where it is plugged into a USB port so that data can be uploaded. The data are QC'd and formatted by respiratory technicians working in a control center in Atlanta, GA, the report is interpreted by a board-certified sleep physician, and within hours, the diagnosis reaches the original primary care provider. "We have the only home sleep testing product with sleep doctors at the center of a network of 135,000 primary care physicians," Heyniger claims.

Based on the outcome of the test, appropriate treatment considerations are also automatically generated. Finally, an important piece in the future, Watermark will aggregate compliance data from CPAP, APAP (automatic positive airway pressure) and other devices capable of collecting usage data. "It is a complete end-to-end platform for screening, diagnostics, and, ultimately, therapy," according to Heyniger.

Watermark's solution fits within the \$250 reimbursement level per home sleep test established by CMS, and saves payors the \$2,000 to \$3,000 that sleep laboratories charge for polysomnography, once the only option. (Heyniger points out that Watermark also saves patients the significant co-pay on such an expensive procedure – 10 to 20% of \$3,000 out of pocket.)

To sell what is essentially a complicated service to primary care physicians, Watermark has developed an innovative business

model. The company employs distributors who call on physicians every day for their routine supply needs to sell the ARES device and the \$75 test kits. One kit is used per test (able to cover one to three nights of monitoring), and the cost includes a disposable head band, electrodes, a nasal cannula, access to the Watermark Web portal, automated scoring and scoring by a registered sleep technologist. Essentially, the model allows distributors to sell a service in the form of a product that they can drop off, just as they do with other medical supplies.

Watermark has signed up three national distributors: **PSS World Medical Inc.**, **McKesson Corp.** and **Henry Schein Inc.**, covering the primary care market with a combined total of 1,750 sales reps. To date, the company also has close to 200 million covered lives under contract with companies like United Healthcare Corp., Aetna Inc. and Cigna Corp.

Watermark got to this point having raised \$30 million in private capital, \$15 million provided by information technology company CA Technologies. Watermark raised another \$6 million from Ballast Point Ventures in September of this year. Heyniger says the company was able to be efficient with its capital because its founders have done this before at CardioNet and PDSHeart. "We have deep domain expertise not just in devices and software, but we also understand workflow and the provider experience, specifically the challenges that doctors have with payments and denials."

Heyniger points out, however, that unlike CardioNet (or home sleep testing company **Sleep Solutions Inc.**) Watermark is not an independent diagnostic testing facility (IDTF); it sells directly to doctors, and doctors bill insurance companies. "The doctor makes the determination about which patients to test; we are the workflow piece, and that enables Watermark to be in the therapy business [without conflict of interest]." By this time next year, Heyniger estimates that Watermark will be testing more than 250,000 patients, many of whom will need CPAP, APAP, an oral appliance or even surgery, he says.

Watermark doesn't see itself putting the sleep testing laboratory industry out of business. Heyniger acknowledges that specialists operating at such facilities will still play an important and necessary role in diagnosing patients with complex disease and co-morbidities. Because of the bottlenecks in diagnosis today, in fact, it turns out that 70% of the patients who sleep centers diagnose tend to have more severe cases of obstructive sleep apnea, according to Watermark's data. Watermark simply aims to grab a large share of the 90% of the patient population that is not yet diagnosed and may not yet have severe disease so people can be treated to stave off harmful long-term complications.

VENTUS MEDICAL FINDS INSPIRATION IN EXPIRATION

With a simple, non-invasive, disposable device, Ventus Medical believes it will be able to treat the entire continuum of sleep disordered breathing from snoring to severe obstructive sleep apnea. They've devised a treatment that is intended to fit into current and evolving physician referral patterns in the US. At the same time, the company feels it is the first sleep apnea company with a product that also has the right combination of attributes to serve millions of

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-Sean Heyniger**

patients in emerging global markets.

Ventus was founded by Rajiv Doshi, MD, a consulting assistant professor at Stanford University and the executive director of the Stanford-India Biodesign program, a collaboration between Stanford University and the government of India struck with the goal of promoting medical device innovation in India. Stanford-India Biodesign is an expansion of the original Stanford Biodesign program directed by eminent interventional cardiologist Paul Yock, MD. (See “*Grad School for Device Entrepreneurs*,” START-UP, June 2005.)

Doshi says that during his two and a half year stint as a principal at De Novo Ventures, a number of surgical devices targeting obstructive sleep apnea came across his desk. The more he learned about sleep apnea, he says, the more he became convinced that any surgical solution would only realize a small fraction of the global treatment opportunity. “I was always of the mindset that a device had to be non-invasive to be widely applicable, especially for a condition as common as sleep apnea.” Doshi, a non-practicing physician who also has a couple of degrees in engineering, turned his attention to the physiology of breathing to find a solution.

In 2004, Doshi invented the Ventus Medical product called *Provent*, a device that maintains positive airway pressure in a unique way. The conventional CPAP devices keep the airways open by providing pressure during both inspiration and expiration. *Provent* instead works by creating only expiratory pressure (also known as EPAP, or expiratory positive airway pressure).

Doshi says he worked on a prototype of the device in his spare time for almost a year, trying it out on himself to see if it would stop his own snoring. Satisfied that it did, he had only to walk across the hall to show his invention to his venture capital colleagues, David Mauney, MD, and Jay Watkins at De Novo. They liked the idea, and thus the first million dollars was raised for Ventus.

Ventus used its initial funds to further develop the device and gather supporting clinical data, and it was off and running. To date, Ventus has raised \$62 million, including investments from De Novo and Mohr Davidow Ventures. The company’s Series D round, which was led by Johnson & Johnson Development Corp., brought in a total of \$40 million, with the last tranche closing earlier this year.

Provent consists of a pair of single-use devices, one to be placed over each nostril. Each device is a one-size-fits-all adhesive patch that attaches around each nostril; within the patch are two tiny valves that remain open on inspiration and create resistance upon exhalation.

Ventus will offer products in multiple resistance levels; the company is first focusing on the obstructive sleep apnea

market, with products that create greater resistance upon exhalation, following up with a lower-resistance product to be sold over-the-counter for non-apnea patients who snore. Both are large markets; snoring affects approximately 28% percent of women and 44% of men who are between the ages of 30 and 60.

“The operation of *Provent* is counterintuitive,” says Philip Westbrook, who is chief medical officer of Ventus, “but it works.” Breathing is a three-part cycle, explains Westbrook, divided between breathing in, breathing out, and a pause. It is during the pause that the airway is the narrowest, and, in susceptible patients, most likely to collapse.

As noted, CPAP prevents that collapse by increasing air pressure inside the airway with a piece of durable medical equipment that uses electricity and a face mask. In contrast, with a disposable mechanical device, Ventus maintains airway pressure by increasing pressure only during exhalation. With a set of devices in place in the nostrils, the patient still has positive airway pressure at the point where he or she is taking the next breath. Westbrook says that the precise mechanism of action of the device is not known, but that *Provent* delays expiration, eliminating the pause in the breathing cycle and increasing the volume of the lungs, likely causing them to pull down on the trachea and stiffen the upper airway, making it resistant to collapse.

As a small, plastic, single-use disposable, *Provent* looks like a simple consumer device, but CEO Peter Wyles points out that it’s

Exhibit 3

A Brief History Of Sleep Apnea

1956: Burwell et al. publish their classic description of obesity hypoventilation, called “Pickwickian” syndrome.
1966: Gastaut et al. perform polysomnography in “Pickwickian” patients, identifying obstructive sleep apnea for the first time.
1978: Tracheostomy recognized as effective treatment circumventing upper airway collapse.
1980: Colin Sullivan of the University of Sydney invents CPAP.
1981: Uvulopalatopharyngoplasty (UPPP) introduced as treatment for OSA.
1982: Tongue retaining device for obstructive sleep apnea first described.
1988: Initiation of Wisconsin Sleep Cohort Study, an ongoing longitudinal study of the causes, consequences and natural history of sleep disorders.
2001: Study in Switzerland finds mandibular advancement devices effective against OSA.
2001: Publication of the “Sleep Heart Health Study,” a multicenter, longitudinal study testing whether sleep-disordered breathing is associated with an increased risk of coronary heart disease, stroke, all-cause mortality, and hypertension.
2008: CMS reimburses home sleep testing as a basis for prescribing CPAP. Requires 12 weeks of CPAP compliance testing.
2008: First positive expiratory pressure device (<i>Provent</i>).
2009: CMS expands national coverage for home sleep testing, outlines four categories of home sleep tests.

SOURCE: “History of the Development of Sleep Medicine in the United States,” *Journal of Clinical Sleep Medicine* 2005;1(1); Company interviews

a medical device, available only by prescription, and Ventus has taken care to validate the product with clinical trials. At the annual meeting of the Associated Professional Sleep Societies in June 2010, Ventus presented its positive results from a 250-patient randomized, sham-controlled trial conducted in 19 centers across the US. The duration of the trial was three months and all studies were conducted in the rigorous setting of the sleep laboratory. According to the study's results, Provent reduced the AHI index (apnea-hypopnea index, a measurement of the number of breathing pauses per hour of sleep) by a median of 53% in a group of mild, moderate and severe patients. "Working with key opinion leaders in sleep medicine and ENT surgery, we have gone down the conservative academic path with a series of rigorous clinical studies," Doshi says. The device received 510(k) clearance in 2008 for all levels of severity of obstructive sleep apnea, and the company is conducting a targeted launch with sleep physicians and ENT surgeons.

PROVENT IN PRACTICE

According to study results, Provent may be less effective in reducing the number of breathing events than CPAP in some patients, but compliance with the device is very high, and its ability to dramatically reduce snoring while treating sleep apnea provides the user and sleep partner with additional benefits, according to Wyles. However, Wyles says that Ventus isn't looking to supplant that traditional standard. The company believes it has a ready and waiting large initial market in the patients who have been diagnosed and for whom CPAP has been prescribed but who have fallen away from the therapy. Wyles points out that for payors, CPAP has a high cost of failure. "If the patient relegates this device – this blower, and all its components – to the garage, that money is gone." Provent, in contrast, has a very small up-front investment. Provent may also serve as an ancillary product for compliant CPAP users that better fits lifestyle needs, such as being able to travel without carrying and relying upon an electrical machine.

Ventus believes it offers sleep medicine physicians an alternative to CPAP for their patients, one that is non-invasive and doesn't have to be custom fitted and manufactured, a requirement for many dental appliances. But it also has the potential to capture a new and large market by offering primary care physicians the chance to help their patients at the point of care. For many of the patients with mild to moderate sleep apnea, CPAP may be overkill. Because it is a non-invasive, disposable device, Ventus believes Provent could become the option of first resort – the patient could take it home and assess its benefit.

The primary care market has always been difficult for medical device therapies, with their need for training and in-servicing support, but with its once-daily disposable model, Provent may be amenable to the pharmaceutical detailing model, where reps drop off samples and literature and there is little need for follow-up with the patient. Ventus sees pharmaceutical companies as potential future

partners, as well as medical device companies operating in respiratory disease, sleep medicine, cardiovascular disease, and diabetes.

To these future potential strategic partners, Doshi says Ventus offers one key advantage: the type of product that can penetrate emerging global markets in India or China, for example. In Doshi's

view, "A lot of medical device companies feel that these are lands of opportunity, but they don't really have the kinds of products that are broadly relevant in these emerging markets." CPAP, for example, as a piece of equipment that requires a continuous supply of electricity, has obvious drawbacks in the BRIC countries. Doshi points out that in India, roughly 90% of people don't have health insurance, but at the same time, 20% of the urban male population has sleep apnea. "I expect Provent and ultimately our snoring product will have great applicability outside the US, and that piece alone is important for strategic partners, since there are few therapies that have this kind of broad applicability," he suggests.

WHAT'S NEW IN CARDIOVASCULAR CARE? SLEEP APNEA

As noted, sleep apnea in all of its forms affects a substantial portion of the general population. But there are certain patient populations where the prevalence is even higher, people with heart disease, for example. These patients are already under the routine care of clinicians who might once have shrugged off symptoms of sleeplessness and fatigue as a natural result of heart failure or some other underlying disease. Increasingly, cardiologists are becoming double-boarded in sleep medicine because of the known association of sleep apnea as a risk factor and a co-morbidity that accelerates other disease processes. It is these kinds of frontline physicians that the newer products for diagnosing and treating sleep apnea at the point of care can help. One such physician is Lee Surkin, MD, president of Cardiac Wellness Specialists and Carolina Sleep in Greenville, NC. (Surkin is also on the medical advisory board of Watermark Medical.) Surkin notes that the prevalence of sleep apnea is closer to 72% in stroke patients, 75% in heart failure patients and 50% in patients suffering from atrial fibrillation. "I got into this field because I recognized the close link between cardiovascular disease and sleep apnea, and I am therefore able to provide an additional layer of synergistic care to my patients," he explains.

William Abraham, MD, director of cardiovascular medicine at **Ohio State University Medical Center**, also pays close attention to the link between heart disease and sleep apnea. Abraham says Ohio State has created an integrated sleep-heart program where all heart failure patients are screened for sleep apnea. "No heart failure patient would ever get an evaluation without some testing for ischemic heart disease, yet nationally, fewer than 5% of heart failure patients ever get evaluated for sleep apnea, even though 50 to 80% of them have it," Abraham says.

In his view, the evidence is compelling that sleep apnea has a major impact on outcomes in heart failure. "Sleep apnea is not an innocent bystander; we now have good data to show that it is a very powerful indicator of increased risk for morbidity and mortality. At a mechanistic level, apnea stimulates vasoconstriction and neuro-

**"I expect Provent and ultimately our snoring product to have great applicability outside the US, and that piece alone is important for strategic partners..."
-Rajiv Doshi**

hormonal activation; it contributes to pathological remodeling, and clinically it has been shown that you are more likely to die if you have heart failure and sleep apnea than heart failure alone, so we have to find better ways to find it and treat it.”

Heart failure patients with sleep apnea divide roughly into two equal halves, those with obstructive sleep apnea and those with central sleep apnea (although a certain number have both types). To date, all sleep apnea therapies have been focused on OSA, leaving a gap in the treatment of central sleep apnea, one that Cardiac Concepts Inc. hopes to fill with a neurostimulation device. Founded around an idea that came from heart failure clinician Howard Levin, MD, and inventor/engineer Mark Gelfand (serial entrepreneurs who now run an incubator called Coridea Inc.), Cardiac Concepts recently raised \$27.2 million in a Series C round. According to an SEC filing, the company's investors include Affinity Capital Management, Polaris Venture Partners, Three Arch Partners, Versant Ventures and Accuitive Medical Ventures. Medical device entrepreneur Dale Spencer, who founded ev3, among other prominent and successful and device companies, is on the board.

Bonnie Labosky, CEO of Cardiac Concepts, formerly led the heart failure business at Medtronic. She explains that although central sleep apnea results in the same harmful breathing pauses as OSA, it's a different disease with a different origin. In patients with OSA, blockages in the upper airway cause episodes of apnea and hypopnea. In central sleep apnea, because of heart failure or neurological causes (following a stroke or brain trauma) aberrant signaling mechanisms are at fault. “Normally the brain regulates breathing by recognizing the balance of carbon dioxide and oxygen in blood as it flows through the respiratory control center of the brain, in the medulla. When that gets out of balance, the brain causes us to breathe faster or slower, as necessary,” Labosky explains. In central sleep apnea, she says, the signals are processed incorrectly. “The breathing pattern becomes disordered, and heart failure patients experience a pattern of hyperventilation followed by apnea – no breathing, or very shallow breathing – hypopnea.”

In central sleep apnea, Cardiac Concepts is operating without much competition. ResMed and Respironics have developed ASV (Adapto Servo Ventilation) devices, offshoots of CPAP, and are testing them for central sleep apnea. Cardiac Concepts has developed a fully implantable neurostimulation device, and after getting good acute results, has started a pilot study on the device in Europe while it awaits regulatory approval to start clinical trials in the US.

The Cardiac Concepts' *RespiCardia* system stimulates the phrenic nerve to cause the diaphragm to contract and expand, allowing a patient to experience more normal breathing according to a proprietary stimulation algorithm. Labosky points out that CPAP and its variants, which blow air into the patient, are not physiologic, and are not tolerated well by most patients with heart failure.

In addition to its proprietary algorithm, Cardiac Concepts' platform also includes the method by which it is able to transvenously stimulate the phrenic nerve with specialized leads. Labosky describes the procedure as being “just like implanting a pacemaker, very straightforward,” and, as such, it is a good fit in the heart failure armamentarium of cardiac resynchronization and primary prevention defibrillators.

Abraham observes that there is a great deal of fragmentation in the field of sleep medicine. Heart failure, however, with the highest prevalence of sleep apnea, may represent the low-hanging fruit for

sleep apnea companies, and a focal point for integration in the field. Abraham points out that once cardiologists appreciate the clinical value of something, and once financial incentives are in place, their willingness to adopt new devices has been historically good. “Look at nuclear medicine perfusion studies and Holter monitors; once these became established, cardiologists brought them into their practices and became drivers of utilization,” says Abraham. Despite the high prevalence of sleep apnea, sleep medicine has been seen as somewhat of a boutique arena. “Now you will have a bunch of cardiologists clinically and financially motivated to treat this condition,” he suggests.

Lee Surkin would like to see that as well, but he says that from the cardiologist's perspective, there are still some major gaps. “As a cardiologist, my practice is based on clinical and academic research studies including tens of thousands of patients, which help create practice guidelines. When we look at the relatively young field of sleep medicine, the studies have had 50 to 200 patients. Statistically speaking, we are talking about a huge discrepancy,” he argues. Surkin is calling for his colleagues to become members of the newly created American Academy of Cardiovascular Sleep Medicine, a society Surkin formed to support clinical and academic research needed to refine practice guidelines for internists and sleep physicians, and to provide advanced education for primary care doctors, cardiologists, and sleep physicians taking care of cardiac patients with sleep disorders.

SLEEP APNEA: THE NEW CHOLESTEROL

Watermark Medical's Sean Heyniger believes that the clinical community is still at an early stage in terms of recognizing the potential benefits from treating sleep apnea. In his view, “Sleep apnea is like cholesterol was 30 years ago,” sharing with cholesterol a status as both a risk factor and an agent that worsens other progressive and chronic diseases. Such recognition begins with tools for diagnosing and treating the disease, and the process of education that goes hand in hand with those new products. Start-ups are bringing the care of sleep apnea into a wider arena, and that will be good for patients, payors, and medical product companies. These will now have a new framework for offering non-invasive, less-invasive and surgical treatments for a continuum of patients with a serious condition that must be kept in check to prevent other life-threatening diseases. Companies such as those profiled here have the potential to push the evolution of the field of sleep apnea to a new level, in their continuing search for the right products and business models for an emerging disease.

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