Evaluate Vantage

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Interview – Respicardia looks to the US

Elizabeth Cairns

When one company's attempt to treat central sleep apnoea in patients with heart failure results in a significantly higher death rate in the treatment arm, other groups might fight shy of attempting to treat the disorder. Not Respicardia. In the wake of ResMed's high-profile rout last May, Respicardia has persevered and scored a win in its US pivotal study – launch of its Remede neurostimulator could come next year.

"We create negative pressure," says Bonnie Labosky, Respicardia's chief executive. "The diaphragm pulls down, and the pulling down of that muscle sucks in air. We've imitated the physiologic mechanism of breathing." As ever, though, approval is only half the fight: to succeed commercially, Respicardia will need to get payers on board.

Central sleep apnoea (CSA) is thought to arise as a consequence of heart failure – around a third of heart failure patients have the disorder – but it may also occur as a result of stroke or even sleeping at a high altitude.

In Respicardia's favour is that it treats CSA using a totally different technology to ResMed's. ResMed was using a form of continuous positive airway pressure (CPAP), in which the patient wears a mask attached to a ventilator that blows air into their lungs (*ResMed crashes after death rate increase, May 15, 2015*). CPAP was developed to treat the obstructive form of sleep apnoea (OSA), which Ms Labosky says has an entirely different aetiology to CSA.

"Central sleep apnoea is neurological in the sense that the origin of the problem is in the brain. In OSA the origin is in the muscles of the throat. They're usually obese patients and when they lie down the muscles of the throat collapse and they obstruct the throat so the patient can't breathe. The mask blows air down the throat to open up those muscles."

It is now thought that this positive pressure approach can put strain on the left side of the heart, harming heart failure patients.

Neuro

Respicardia's technology is a neurostimulator, about the size of a pacemaker, implanted in the upper chest with a wire leading through the veins to the phrenic nerve. Stimulation of this nerve makes diaphragm contract, causing the patient to take a breath.

Though other companies are looking at similar technology, there is no other fully implantable device in the US for central sleep apnoea, Ms Labosky says. The closest is perhaps the partially implanted phrenic nerve stimulator – the battery is outside the body – developed by Avery Biomedical, but that is designed to aid breathing in patients with spinal cord injury.

Respicardia's own system is CE marked and on sale in Germany, Spain and Switzerland. And US approval looks fairly likely following the successful conclusion of its pivotal trial.

The trial enrolled 151 patients with moderate-to-severe CSA, roughly two thirds of whom had heart failure. The Remede system was implanted in all the patients and the device was switched on in 73.

Of the Remede-treated patients, 51% met the 50% apnoea-hypopnea index reduction goal, compared with 11% in the sham group. The primary safety endpoint was also met, with 91% of patients free from serious adverse events associated with the implant procedure, the system itself or the delivered therapy at 12 months.

The full data were presented at the meeting of the European Society of Cardiology meeting in Rome last month and simultaneously published in the Lancet.

"We designed the trial with the FDA and our scientific and physician advisers, so everybody's agreed that if we met the endpoints that's a clinically meaningful result," says Ms Labosky. The data have been submitted to the agency, and while Ms Labosky is reluctant to give a date for approval, the FDA currently takes around 16 months to grant PMAs, so late next year might be plausible.

Partner

In Europe the system is sold by LivaNova under an agreement signed in 2014 with one of LivaNova's predecessor companies, Sorin. The UK group is funding a European post-market study aimed partly at convincing payers.

"The big challenge is reimbursement because it's a brand new product," Ms Labosky says, "but we are having some early success in Germany and Spain in particular." Respicardia is also pursuing a separate health economics study.

Remede costs "in the thousands of dollars", Ms Labosky says, but after the initial cost the system lasts for around five years before the battery needs to be replaced. CPAP – far from perfect in CSA, and actively dangerous in patients with heart failure – has ongoing costs as the machines must be rented and the masks and tubing replaced every six months.

"We think we are cost-effective – for one thing we provide better therapy because we work all night and masks are only used for approximately half the night," Ms Labosky says. Compliance with CPAP therapy is notoriously low.

The company has not yet decided whether to partner for the US market as well. But the agreement with Sorin grants the larger company an exclusive option to acquire Respicardia. A takeover by LivaNova is a distinct possibility – but Respicardia will probably have to get US approval, if not reimbursement, first.

Study	Trial ID
Pivotal	NCT01816776
Treat-CSA (postmarket)	NCT02577445

To contact the writer of this story email Elizabeth Cairns in London at elizabethc@epvantage.com or follow @LizEPVantage on Twitter