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CVRx's Investment In HF And Wider Medtech Industry Set To Pay Off

by Ashley Yeo

CVRx president and CEO Nadim Yared believes his company's second-generation chronic heart failure device could present a serious commercial challenge to the traditional major players in the field. Meantime, with 10 years under his belt as CEO, Yared is focused on building the company, rather than on exits.

- CVRx's second-generation device is about to enter a pivotal trial in the US ahead of an FDA filing for an application to treat heart failure, a market that extends to 5.1 million adults.
- FDA has shown its collaborative qualities in helping CVRx design trials for the PMA class device in novel and innovative ways, and has left the company deeply impressed.
- Company president and CEO Nadim Yared believes that revenues from the Barostim Neo device could become large enough to elevate CVRx among the top four global heart failure companies.
- Not content with merely steering CVRx into the commercial phase for the HF application (Barostim Neo also has an application in hypertension), Yared holds decision-making roles in other organizations, including AdvaMed, which has tapped him for its key post.

Nadim Yared is a consummate networker. Indeed, the device industry entrepreneur who leads private Minneapolis-based *CVRx Inc.* has a lot to network about, as he stewards Barostim therapy for the treatment of chronic heart failure and hypertension onto the US and EU markets.

There, and once established, he is confident that the heart failure device (the first intended application of which was hypertension) will succeed in reaching a part of the market – a large part – that the existing CRT-D devices cannot. On this basis, CVRx would break out of SME status and provide serious competition to the industry's current big three.

CVRx's second-generation *Barostim Neo* is designed to electrically activate the baroreflex, the body's natural mechanism that regulates cardiovascular function. By activating this afferent

pathway, the device reduces sympathetic activity and increases parasympathetic activity to restore autonomic balance.

Ten years in the role of president and CEO of CVRx as of September 2016, Yared presents himself as someone with a broad and deep knowledge of his immediate industry, but also as a champion of the wider industry as it reaches out to payers and other stakeholders on issues of broad market access appeal.

These qualities have made him a key player over many years within the US industry association AdvaMed, alongside his CEO role and other directorships. This industry involvement culminated recently in Yared being designated as AdvaMed's chairman-elect for the next two-year term.

Views On Compliance

Yared's ability to share experiences and give counsel was on display at the ninth annual *Global MedTech Compliance Conference* (GMTCC), held in Dublin, Ireland. There, sitting alongside counterparts from *Olympus Corp. of the Americas* and *Teleflex Inc.* on a panel addressing global compliance issues, the CVRx CEO, head of a US-focused company of 80 staff, assumed the mantle and outlook of a globally much larger player, as he shared his views on key industry developments and requirements.

"The principle of compliance needs to be embraced by the culture of the company from the ground up. We find that as we develop our culture from within, a new set of core values emerges," he told the meeting's 300 delegates. If this sounds like it might have come from someone with a longer industry pedigree, you'd be right: prior to joining CVRx, Yared spent almost 15 years at two industry majors, first at GE Healthcare and then at Medtronic PLC, holding general manager posts in X-ray imaging and navigation, respectively.

The point is that Yared appears to possess antennae that seek out ways to represent the broader industry that also suit CVRx's needs into the bargain. In 2008, two years after taking over at CVRx, he saw that the US device sector needed more support, and decided to throw himself into macro industry developments, just as the global economic downturn was starting to bite.

Eight years on from that, sitting high up in the Convention Center of Dublin, overlooking the River Liffey on an uncommonly warm May day for the Irish capital, Yared related for *In Vivo* the story of how, back in 2008–09, he was inducted into the US medtech lobbying hall of fame.

Perfect Storm

"We had had the 'perfect storm' – the global financial crisis that began in fall 2008, the beginnings of the Affordable Care Act [the PPACA] and, linked to it, the device excise tax. While our industry was supportive of the need to reform health care, we were not supportive at all of how the device excise tax was being brought in, and at the time, we went through a soul-

searching period," Yared said.

There was also pressure to reduce the cost of care by delaying the introduction of novel technology. "The belief was that the delayed launch of new technology would reduce the cost of care. That is the perception of few people, and in fact, the opposite is the truth."

Another element in the mix was the fact that the money flow had frozen for a while, and it had become very hard for venture-backed companies to raise money. There was no liquidity in the market and the cost of getting a company from "A to Z" was increased by a multiple of two, given the rising market access costs in the regulatory and reimbursement/payer fields.

Add to that what the CVRx chief calls a certain "frothiness" – a favorite Yared expression – that was evident among the strategic consolidators when looking to acquire at-risk technologies, and there it was clearly: the perfect storm. He explained: "Over the years, there had been some 'big misses,' where companies had acquired a technology too soon, or the technology had not panned out as expected."

This made the consolidators more risk-averse rather than risk-neutral. "It was indeed the perfect storm for our industry, and I figured that it would be very hard for a small firm like CVRx to be able to succeed without removing some of these obstacles."

Working Up The AdvaMed Ladder

Yared joined AdvaMed in 2008, as a rank and file member, in order to participate in the association's meetings. But once in the door, he helped create a new interest group – a working group called the Emerging Growth Companies Council (EGCC). "Five of us were very vocal about it, and we started to grow the number of participants and also stepped up engagement with AdvaMed."

"Under the leadership of Michael Minogue [CEO of Abiomed Inc.] and Ashley Wittorf [AdvaMed], we converted EGCC into a larger body with its own separate board of directors. That was four years ago. The group has now evolved to a point where it can manage its own policies and define its own strategic plans and agenda. In another developmental step, we rebranded it to AdvaMed Accel. That was during my time as chair in the last 24 months."

Nadim Yared

This was all happening at a time of structural disconnect between AdvaMed and fellow US indust

“We, as an industry, were taken advantage of because we were divided. Some politicians sought t

] manufacture CRT, but their devices can only address 25% of HF patients," said Yared. "We have a product that can address the remaining 75% alone – and that does not even include the business to be done with the hypertension device. The market potential is huge, and it requires a lot of muscle and big shoulders to be able to carry and develop it. It is hard, but doable, and it will require a lot of work and sweat."

Strategy For Market Penetration

Yared won't say when CVRx could be joining the big three club in heart failure, as you might expect. "It's a step by step thing. Right now we are commercializing in Europe, where we are focused on getting the product reimbursed country by country, building awareness of the therapy as we go."

Barostim Neo is already reimbursed in Germany under the ZE code (for certain specific procedures and treatments, the supplementary payment – Zusatzentgelt – is possible).

And in the US, it was designated an Expedited Access Pathway by FDA. "We have just started the US enrollment for our pivotal HF trial," Yared said.

Unique Partnership With FDA On Barostim Neo

A PMA product, the Barostim Neo System has unique features. The system consists of a single extravascular lead that is placed on the carotid sinus, an implantable pulse generator (IPG) that is placed above the collarbone and stimulates 40 times more frequently than a pacemaker, and a wireless programmer system that allows for non-intrusive, fully customizable patient follow-up. The procedure to place the lead and IPG is minimally invasive, taking about an hour and a half, skin to skin. In Europe, where Barostim Neo is CE marked, the therapy is used to improve the quality of life of HF patients, demonstrating consistent benefits to those who are not eligible for CRT. And now in the US, the long-term effects of restoring autonomic balance in heart failure patients will soon be observed via the upcoming pivotal trial.

"It is very exciting, and we are conducting the study in two stages, where each stage leads to a separate FDA approval," said Yared. He stresses that the trial has been designed *very* jointly with FDA. "It became a very collaborative, interactive exercise, once FDA determined that our product line has the potential to become a useful treatment, has no known substitutes and meets an unmet need in heart failure – a debilitating and life-threatening condition."

"I did not expect this level of FDA attention, but they were providing

us with real, genuine help." – Nadim Yared

Yared continued, "FDA has provided a lot of resources to support and guide us in the design of the trial. So we must give the Center for Devices and Radiological Health [CDRH] kudos for that – they did a really good job." The CVRx chief almost marvels at the path of events with US authorities. "In 25 years in the industry, I have never seen such a strong collaborative, interactive effort."

"With FDA, it's usually a very different process. Normally, you submit proposals and they comment on them," he said. But he was pleasantly surprised by the experience. "This time, FDA came forward with creative ideas, and we would come up with others. We evaluated them on a weekly basis. I think this program will be a landmark for FDA in terms of how can we reduce the time to market by a year or maybe even two – not by cutting corners, but by working very closely and using advanced scientific tools, such as Bayesian statistics, to get to answers faster and in a less burdensome way." He continued: "I did not expect FDA to provide this level of attention, but they have provided us with real, genuine help."

If I Had My Time Over Again…

Yared will be celebrating 10 years in the CEO role in September 2016. He is proud of his achievements, but is not above taking advice. "Is there anything I would have done differently? It would be presumptuous – stupid even – for anyone to look back and not learn from the past; you can always do better," he says. Using another favorite expression, he adds, "With hindsight 20/20, there are many other things you could have done. But it's often hard to know that at the time."

One regret is the pace of market rollout at CVRx. "I would have wanted the product to have been already approved in the US and accessible to US patients. We should have gone much faster," says Yared. The reason, he explained, was that it takes time for some innovative technologies to mature. "We had a first-generation device [the Rheos] that demonstrated the impact of the mechanism of action and showed that the therapeutic targets we are going after are very potent, and safe. But the apparatus itself was suboptimal." That pushed CVRx back to the drawing board in 2010–11, whereafter it developed the second-generation device, Barostim Neo.

More Funding To Come As Rivals' Fortunes Mixed

The last time *In Vivo* sat with Yared coincided with CVRx's Series F funding. That was in December 2013, and Yared had said back then that it would be the last round of funding. (*See*

(Also see "*CVRx: Pioneering Hypertension And Heart Failure Devices – Big Markets Take Big Funding*" - In Vivo, 20 Dec, 2013.).) And although that Series F *was* the last to date, the situation for CVRx has altered, and even while we spoke at the GMTCC, Yared was pondering new funding options for CVRx.

He explained that one of the biggest differences between then and now is the change in market prospects for certain rival technologies that were being developed to exploit the market CVRx is entering. "We have seen the successive failures of competing neuromodulation technologies with dissimilar mechanisms of action – renal denervation [Medtronic's Simplicity III], vagal nerve stimulation [Boston Scientific's NECTAR-HF]." Medtronic's DEFEAT-HF trial of spinal cord stimulation for the treatment of heart failure, in fall 2014, was similarly disappointing: the implantation of a spinal cord stimulator was not associated with clinical benefit or improvement in outcomes as a treatment for advanced heart failure.

"While these outcomes have thrown a veil of uncertainty over the field of neuromodulation for the treatment of cardiovascular disease," said Yared, "it just becomes ever more important for us to remind our stakeholders how Barostim Neo functions differently, as it's still the only device designed to work at the very top of the autonomic cascade. We also saw the need to raise more money to conduct a pivotal trial before a possible IPO or exit, as from a financial point of view, the market became a bit more risk averse." Yared sees all this as a test, of sorts. "When we went to raise the Series F, the goal was to conduct a Phase II trial and get the data – which are 'phenomenal.' Execution of the trial was within our control, but the rest of the environment was not, and so, as we see it, our ability to react is being tested," he said.

Clearing the field of opponents is not always the straightforward ride it may seem. "When a competitor abandons a market, it is good and bad. Being alone in the market requires you to do more 'heavyweight lifting' to convince regulators, payers, physicians, consumers and users to adopt the technology. When two or more do it together, it's easier," said Yared.

Having said that, being a unique player in the market has its own advantages. "I will not say I wish for more competitors, but the disappearance of those competitors in a spectacular way can be seen as a burden on the entire industry – not just for the person or player directly affected," Yared added. For the time being, CVRx aims to collect enough clinical and health economic evidence to prove the points it wants to make with Barostim Neo – CVRx's flagship brand.

Right now, and like his "predecessor-in-waiting" at AdvaMed, Yared has his plate more than full, with the Barostim Neo pivotal trial enrolling now, funding to secure and launch plans to shepherd into place. If high ambition, a cool head, a realistic outlook and an intense work rate with a potentially ground-breaking technology should be any yardstick, this Minneapolis company must be worthy of close attention in the coming 24 months.