Executive Summary

Drug-coated balloons were once thought to be an unnecessary innovation because of drug-eluting stents. With DES no longer seen as the panacea for vascular disease, balloons could re-emerge as the next major technology platform, and Lutonix is leading the race to bring them to the US market.

By Stephen Levin

The idea of applying a drug to an angioplasty balloon to treat vascular disease is not new, but turning that notion into reality has proven to be more difficult than many expected.

The development of drug-eluting stents initially appeared to obviate the need for drug-coated balloons, but the late-stent thrombosis risk, along with the ineffectiveness of DES in areas like peripherals have revived interest in balloon-based approaches.

Lutonix has developed an innovative carrier molecule to facilitate rapid and effective drug transfer from the balloon to the vessel wall, while minimizing the amount of drug used.

The company is the first to receive an IDE approval for a drug-coated balloon and is starting its US pivotal trial, giving Lutonix a significant competitive advantage.

During the peak of the drug-eluting stent (DES) wave in the early to mid 2000s, cardiovascular conferences actually entertained discussions as to whether the era of significant innovation in interventional technology for treating vascular disease had been brought to an end by DES, leaving only small niche
opportunities remaining. Since then, the risks of late-stent thrombosis, concerns about the cost and overuse of drug-eluting stents, as well as evidence of clinical areas such as peripheral vascular disease where DES have been ineffective, have shown that it was premature to think drug-eluting stents would prove to be the panacea for vascular disease that some thought they would.

Indeed, some industry executives and clinicians believe that we are about to see the emergence of the next major platform technology to treat vascular disease, following angioplasty balloons, bare-metal stents, and then drug-eluting stents. That is drug-eluting, or as Lutonix Inc. prefers to describe it, drug-coated balloons (DCBs).

The notion of applying drug to an angioplasty balloon to treat vascular disease may sound like a Back To The Future kind of idea, and in fact, the concept is not new. It was tried unsuccessfully back in the early 1990s for coronary disease. The development of drug-eluting stents at first appeared to obviate the need for a drug-coated balloon. However, a small but vocal group of physicians have long argued against therapies that require a permanent implant, and the clinical community as a whole recognizes the ideal long-term value of an implant-free approach such as a balloon-based technology. The emergence with DES of the risk of late-stent thrombosis and accompanying required extended dual anti-platelet therapy (DAPT), along with the failure of drug-eluting stents to effectively treat problems such as peripheral disease and in-stent restenosis (ISR) have revived interest in balloon-based approaches. Indeed, recent iterations of this approach appear to have overcome many of the technological hurdles that plagued earlier efforts, and are focused largely on applications where drug-eluting stents have proven ineffective.

That is the strategy being employed by Maple Grove, MN-based Lutonix, which is the second start-up for interventional cardiologist/entrepreneur Dennis Wahr, MD, president and CEO. The company appears to have developed an innovative carrier molecule designed to quickly and effectively transfer paclitaxel from a balloon to a diseased arterial site in the short time that the balloon is inflated. Lutonix recently became the first company to receive an IDE approval to begin a US drug-coated balloon pivotal trial, making it the clear leader in the race to bring this next-generation interventional technology to the US.

**Getting The Entrepreneurial Bug**

Having spent 15 years as a practicing interventional cardiologist, Dennis Wahr is very familiar with the advantages and disadvantages of drug-eluting stents. Wahr started the interventional cardiology program at St. Joseph Mercy Hospital in Ann Arbor, MI, before being bitten by the device entrepreneurial bug. He has always been interested in device technology - Wahr was an original member of the medical advisory board of SciMed Life Systems, a pioneer in interventional cardiology devices that, through its acquisition, became the basis of Boston Scientific Corp.'s cardiology business. [See Deal]

Wahr's interest in starting his own companies was fueled by his work with successful device entrepreneur Dale Spencer, a founder of both SciMed and ev3 (now part of Covidien Ltd.). [See Deal] "I loved the creative process of moving the technology bar forward and that naturally led to me wanting to do that myself, so I made the leap from medicine to entrepreneurship," Wahr explains. "People often ask how I made that transition, not knowing much about business, and the key is having a mentor; mine was Dale Spencer."

In 2001, Wahr, Spencer and another SciMed alum, former CEO Michael
Berman co-founded Wahr's first company, Velocimed, which developed a number of interventional devices, including a PFO closure system and an embolic protection device. Although the company quickly produced several innovative products, Velocimed was actually launched without having any specific product in mind, such was Spencer and Berman's faith in Wahr's entrepreneurial skills. That faith was rewarded just four years later when the company was acquired by **St. Jude Medical Inc.** [See Deal]

"When Velocimed was sold, I knew I would do it again as soon as I could identify the next worthwhile project," says Wahr, who adds that his goal is to launch three device start-ups. He remained with St. Jude Medical for six months following the Velocimed acquisition and then became a partner with RiverVest Venture Partners, a Velocimed investor, with the understanding that he would move on when he found the appropriate opportunity.

Wahr didn't have to wait long. In 2006, Lixiao Wang, PhD, who had also been at SciMed, Boston Scientific, and ev3, approached Wahr with an idea about applying a drug coating to an angioplasty balloon to treat restenosis. Wang is a chemical engineer who played a significant role in developing numerous interventional cardiology products for SciMed and later for Boston Scientific. Wahr estimates that Wang has more than 115 issued US patents, mostly in cardiology.

At that time, the idea of a drug-coated balloon was largely theoretical, confined to early stage research and preclinical work. Indeed, 2006 was the heyday of drug-eluting stents with adoption rates at their peak pushing 90% in the US. The late-stent thrombosis scare (in terms of being a real risk the level of which was initially overstated) did not hit until later that year, when DES adoption rates would begin a sharp decline. Other than a small group of physicians who had always decried placing a permanent metal implant in patients, the clinical and public perception of drug-eluting stents was that the advantages far outweighed the risks. While acknowledging that an ideal therapy for coronary artery disease would not require a permanent implant, the widespread success and minimal risk up until then of DES meant there was little interest among clinicians or investors in an alternative implant-free approach like a drug-eluting balloon.

Lixiao Wang had left ev3 and was doing independent research sparked by early work done in Germany by Ulrich Speck, PhD, who along with Bruno Scheller, MD, created the first successful drug-eluting balloon (DEB). The idea behind a DEB was not new - the notion of using an angioplasty balloon to deliver drugs to prevent restenosis had been tried unsuccessfully in the early 1990s (not, however, with the current generation of anti-restenosis drugs such as **Taxol** [paclitaxel] and sirolimus, but instead with anti-platelet agents and blood thinners, primarily heparin, designed to prevent thrombosis). "The problem was that no one could figure out how to transfer the drug from the balloon to the vessel wall in the short period of time the balloon is inflated and yet maintain therapeutic tissue drug concentrations over a prolonged period of time," Wahr explains.

**The Secret Sauce**

The idea that Lixiao Wang proposed to Dennis Wahr in 2006 contained the solution to that problem. The challenge is that, when a balloon is coated only with an anti-restenotic drug like paclitaxel (which is also used on the **Taxus** DES) and the balloon is inflated inside an artery, the drug stays on the balloon - it doesn't transfer to the vessel wall in the 30 to 60 seconds that the balloon is inflated. Paclitaxel and other drugs work so well on a drug-eluting stent because the drug is embedded in a polymer that gradually elutes the drug into the vessel wall over several weeks.

Wang approached Wahr with the idea of creating a drug-coated balloon where the drug, using a unique coating technology that Wahr and his team developed, would be able to transfer from the balloon to the vessel wall in 30 to 60 seconds.
According to Dennis Wahr, “Lixiao Wang recognized the crucial requirement for a carrier molecule to get paclitaxel to transfer from a balloon to tissue in 30 seconds. The carrier is the secret sauce.” And Lutonix is looking to keep its carrier (or excipient) secret for as long as possible, declining to identify the substance or its chemical composition.

The different process by which the paclitaxel comes off the balloon, as opposed to the way it comes off a stent, also accounts for why the company prefers to refer to its Moxy device as a drug-coated, rather than drug-eluting balloon. "Unlike a DES, the drug is not eluted from the balloon itself," Wahr explains. "During the initial angioplasty inflation, the balloon simply transfers the coating to the endoluminal surface of the artery where it forms a reservoir from which the drug is eluted over time." The result: the drug is essentially transferred in a few seconds from the balloon to the tissue. Wahr adds, "In fact, if it were more elegant sounding, we’d call it a drug-transfer balloon because that is actually what happens," noting that Bruno Scheller shares his preference for the term drug-coated balloon.

When Wang approached Wahr with his DCB idea in 2006, the two had only met briefly before. What drew Wang to Wahr was the success of Velocimed. Wahr admits to being initially skeptical that Wang's idea would work. "My big concern was how would you get enough drug in the tissue that fast, and Lixiao convinced me by explaining the role of the carrier molecule," Wahr says. With that question resolved, in late 2006, Wahr and Wang agreed to launch Lutonix, and Wahr left RiverVest to start the new company, which was officially founded in April of 2007 and initially financed by a small seed round from RiverVest.

The timing of Wang and Wahr's decision to form the company proved fortuitous on two fronts. First, the late-stent thrombosis issue in 2006 highlighted a potential risk of DES and triggered increased concern regarding the overuse of drug-eluting stents, primarily for off-label indications. This sparked newfound interest in alternative approaches like drug-coated balloons that would reduce the thrombosis risk without using a permanent implant thought to trigger thrombosis. Also, shortly after the two decided to start the company, the first major article on drug-coated balloons, written by Bruno Scheller, appeared in The New England Journal of Medicine, reporting the results of the Paccocath ISR study, validating the use of paclitaxel on a DCB developed by B. Braun Melsungen AG to treat in-stent restenosis. (The Paccocath balloon uses a combination of paclitaxel and the hydrophilic contrast agent Ultravist [iopromide], which Ulrich Speck invented, to transfer the drug from the balloon to the vessel wall.) According to Wahr, "That was such a stunning paper because it proved that Lixiao was right about the effectiveness of paclitaxel on a balloon, which made it easier for us by establishing a clinical basis for this approach, one that we believed could be improved through use of our carrier molecule." The timing was particularly good, he adds wryly, "because we had already decided to start the company at that point."

The article was also important in helping Wahr to fund Lutonix. Kevin Wasserstein of Versant Ventures, which led the company's Series B financing, points out, "The New England Journal article demonstrated that Taxol had the potential to effectively be delivered on a balloon. It was encouraging because for years there have been myriad different technical approaches that have been unsuccessful, causing many people to say it couldn't be done."

Dennis Wahr found that raising Lutonix's Series A funding was surprisingly
easy. Drawing on his Velocimed experience, the first venture firm he contacted was US Venture Partners, which had wanted to invest in Wahr's prior company, only to be turned down. "Velocimed had the luxury of getting a number of good term sheet options, so we turned USVP down, but I was very impressed with Jon Root's presentation, so he was the first one I called for Lutonix, and after one presentation, he agreed to do the deal," Wahr recalls. In addition to USVP, RiverVest, Wahr's former firm, also invested in the Series A financing, with the two firms splitting the $5 million round, which closed in April of 2007.

**The Science Comes First**

In building Lutonix, Dennis Wahr drew on the same philosophy he used to create Velocimed, which meant focusing first and foremost on establishing a solid scientific and clinical foundation for the drug-coated balloon technology. In fact, just as with Velocimed, Lutonix has remained in stealth mode for longer than many start-ups while the company was concentrating on creating that base of evidence establishing the safety and efficacy of its technology. Shawn McCormick, the company's COO who recently joined Lutonix after a career at Medtronic Inc. and ev3, characterizes this approach as focusing on "making sure we've got the right solution and the right formulation, as opposed to one that is just good enough."

One of the challenges of creating a company to develop drug-coated balloons is the variety of skill sets required, beyond just those of a typical interventional cardiology device company. "It's a lot more challenging than people think to deliver a drug off of a balloon," notes Kevin Wasserstein, which is why it has taken companies 30-plus years since the advent of angioplasty balloons to figure out a safe and effective way of doing it.

Whereas drug-coated balloons are designed primarily to address the shortcomings of drug-eluting stents, the processes of creating the two devices have much in common. Most significant is that DES and DCB companies both require chemical and/or biological - in other words, pharmaceutical - expertise to address the drug component of these combination products, while still requiring the mechanical know-how necessary for the device elements of the product. In that way, drug-eluting stent and balloon companies differ from most typical device firms, most notably in the skill sets of the employees they need to attract, both in terms of R&D and manufacturing, as well as clinical and regulatory. "Any time you're talking about a combination product, that significantly increases the up-front costs required to build that company," says Wasserstein.

In building Lutonix, Dennis Wahr looked to attract an experienced group of senior executives, to keep the company as lean as possible by relying on people who have been through this process before and can thereby avoid many common pitfalls, enabling the most efficient use of limited start-up capital. Unlike Velocimed, however, which relied primarily on typical device skills like those of catheter engineers, Wahr says recruiting employees for Lutonix "was more like a pharmaceutical company in its development phase than a device company because we were looking for chemists and chemical engineers, as well as people with interventional device experience."

Wahr admits to being very selective about the people he hires. In his view, "Hiring is where a lot of start-ups make mistakes because they aren't as discerning as they should be and they end up hiring people just because they are available. The real key to a successful start-up is recruiting the right team and not making compromises on the quality of your people." Wahr is quick to note that Lutonix has been fortunate in its ability to recruit experienced
managers very early in its development. These include Chris Barry, former program manager for Abbott Vascular’s DES program, to head Lutonix’s R&D efforts, Scott Naisbitt, MD, PhD, as scientific director, and Sharon McFadden, DVM, as director of preclinical research.

As to the difficulty of attracting qualified employees to Lutonix in light of the failure of drug-eluting stent start-ups that others may see as similar, Wahr says it’s hard but can be done. “You need to be able to differentiate your technology so that people will recognize the opportunity. Also, the people you recruit will be the ones who have entrepreneurial spirit and want to step outside of the comfort zone of sitting inside one of the big device companies,” he says.

There are three major components of any drug-coated balloon, and, in the case of Lutonix’s Moxy balloon, Wahr acknowledges that two of those are not unique to Lutonix: the balloon and the drug. The company uses a standard OEM angioplasty balloon and, as noted, the drug Lutonix employs is paclitaxel, which is used widely on both drug-eluting balloons and stents. Although paclitaxel use is widespread, sirolimus has actually become the drug of choice in DES. Wahr says Lutonix considered both drugs and has an active preclinical research program investigating use of the limus family of drugs. "But we had a strong preference for paclitaxel because, when we started the company, there already were human data from Europe supporting the use of this drug with balloons, while there was no information on the use of limus drugs," he explains.

What differentiates the Moxy balloon from other similar products is the third component, which is the coating, consisting of the drug and, in Lutonix’s case, its proprietary carrier molecule. While Wahr won’t disclose the carrier molecule that Wang discovered to enable the fast and effective transfer of the drug to the vessel wall, he will say that the company screened more than 225 compounds on the benchtop, performed more than 48 major animal studies involving 120 different coatings, and conducted more than 3,400 angioplasties in pigs before coming up with the final optimized formulation.

Essentially, the carrier is needed to transfer the drug from the balloon to the vessel wall because paclitaxel is hydrophobic and doesn’t dissolve easily in liquid. To transfer the drug, DCBs must use some type of carrier consisting of a hydrophilic substance to make the drug capable of moving from the balloon to the wall of the artery. (Another reason for the preference for paclitaxel over sirolimus is that when one adds a hydrophilic agent to the limus drugs, they become less stable. Because sirolimus is naturally less stable than paclitaxel, Lutonix was concerned that adding a carrier to a limus drug may exacerbate this problem, whereas paclitaxel is a more stable molecule to which one can add a hydrophilic carrier with greater confidence that it will not degrade over time.)

In addition to facilitating the drug transfer, the carrier also governs a number of other factors in a drug-coated balloon. When mixed with the drug to form the balloon coating, the carrier helps regulate the total drug load placed on the balloon that is necessary to deliver a therapeutic dose to the target site. The carrier also helps regulate the amount of drug lost downstream, both during transit of the balloon through the vessel to the lesion and after inflation. Furthermore, the carrier also influences how efficiently the drug is transferred from the balloon to the vessel wall, and the durability and uniformity of the balloon's coating.

Leslie Trigg, the company’s EVP of marketing and commercial strategy, adds that because paclitaxel is also lipophilic, it binds well to the lipids in the artery wall. As a result, the Moxy balloon deposits the paclitaxel in what Trigg calls a
"drug reservoir that remains on the endoluminal surface over a long period of time, from which the paclitaxel is diffused into the tissue." The net effect, she describes, is that balloon inflation "simply transfers the drug from the balloon to the vessel wall; the elution actually happens over a period of months, which is why we prefer to call it a drug-coated balloon."

This reflects a significant breakthrough, resulting from Lutonix's extensive preclinical research to better understand both how a drug delivered by balloon interacts with the arterial tissue, as well as the actual length of time that the paclitaxel remains active. Trigg points out that previous research had hypothesized that the drug was absorbed quickly after leaving the balloon, but the company's research demonstrated otherwise. "Everyone knows that the time the drug remains resident in the tissue is important for maximum effectiveness, but the assumption was that delivering a drug by balloon inflation would not be sufficient, and our research proved that assumption was incorrect," she says.

Indeed, Lutonix's research findings are actually counterintuitive to the previous widely held assumptions. Dennis Wahr explains the process this way: "The simplest way to conceptualize what really happens with a drug-coated balloon is, on the initial angioplasty inflation, the drug is transferred from the balloon surface to the endoluminal surface of the artery, but it's not instantaneously going through the cell wall. The drug actually resembles a coating on the inside wall of the vessel, like stucco on the wall of a house," which is slowly absorbed from the endoluminal reservoir into the tissue over time. An important result of this finding is that the drug absorption kinetics of the Moxy balloon are similar to those of a drug-eluting stent, which are well understood from the many years and studies of that process.

The company's research in this area addresses one of the major challenges facing drug-coated balloon companies: dispelling what previously were seen as dramatic differences between drug-coated balloons and drug-eluting stents in their respective drug distribution curves in the tissue (vessel wall). The perception was that, whereas the tissue concentration curve on a drug-eluting stent starts out at zero and gradually increases to a point at which it is sustained for several months, with a drug-coated balloon, the drug concentration on the vessel wall starts out high and then rapidly declines. That view was largely attributed to the fact that, because stents are permanent implants, those devices have the benefit of being able to deliver drug to an artery over a longer period of time. Since drug-eluting balloons, however, only have that 30- to 60-second window during which the balloon is inflated to transfer drug to the vessel wall in an amount sufficient to safely and effectively treat restenosis, the hypothesis was that most of the drug from the balloon would enter the tissue in a short time following inflation. Lutonix, however, has demonstrated that that hypothesis was only true insofar as measuring the transfer of drug from the balloon onto the vessel wall. In terms of the actual elution of drug from the vessel wall into the cells of the tissue within the vessel, that elution curve in a drug-coated balloon was remarkably similar to that of a drug-eluting stent in that the drug was gradually absorbed over a longer period of time than was previously thought.

Another misconception about drug-coated balloons: that balloons deliver a much higher amount of drug than DES. Dennis Wahr points out that that view arises out of the fact that the amount of drug that needs to be loaded on a balloon is more than the amount put on a stent "because there will always be a meaningful portion of the drug that comes off the balloon and ends up downstream, compared with a drug-eluting stent." But as Wahr notes, that
conclusion is misleading because what’s really important is not the total dose, but the therapeutic dose at the target site in the vessel wall, which is about the same in both drug-eluting stents and balloons.

In the case of the Moxy balloon, drug distribution is another example of the multi-functionality of Lutonix’s carrier. In this case, Wahr explains, the excipient allows for the efficient transfer of paclitaxel to the vessel wall in that short period of time, while minimizing the amount of drug ending up downstream or remaining on the balloon once it is removed. This enables Lutonix to coat the Moxy balloon with only two micrograms per millimeter squared of paclitaxel, whereas the first-generation drug-coated balloons generally used three micrograms. In part, this is because the carrier enables a therapeutic drug dose to be delivered to the deeper layers of the artery with only a sub-therapeutic dose remaining on the outer, endoluminal surface. According to Wahr, “This dose distribution inhibits the neointimal hyperplasia that can lead to restenosis, while allowing endothelial healing at the same time.”

Another difference between the Moxy balloon and many DES is that the carrier agent on the Lutonix balloon is bio-inert and starts to dissipate immediately upon inflation. Most DES, however, use polymeric coatings to gradually elute the drug, with the polymer remaining permanently affixed to the stent. The concern is that the polymer may also be contributing to the inflammatory process that may result in thrombosis, which is why DES manufacturers are looking to use as little polymer as possible, while also searching for biodegradable polymers.

Yet another potential advantage of drug-coated balloons over drug-eluting stents is a shorter duration of dual anti-platelet therapy (DAPT), which both benefits patient safety and reduces cost. The risk of inflammation and thrombosis with DES has resulted in patients requiring extended use of DAPT, typically for at least one year following PCI (percutaneous coronary intervention). Because drug-coated balloons do not involve a permanent implant, prolonged DAPT may not be necessary. Lutonix’s clinical trials required DAPT for 30 to 90 days following treatment with no evidence of thrombosis. In European clinical practice with DCBs, short-duration DAPT therapy is becoming routine, and also has been the standard in virtually all other DCB clinical studies.

According to Wahr, the extensive pharmacokinetics research that Lutonix has done in this area has already proven valuable in helping FDA regulators better understand the company’s technology. He is a strong believer in the value of transparency for a start-up company in dealing with both regulators and investors; to that end, Lutonix has already had 13 pre-IDE meetings with the FDA on its peripheral program alone.

Three Studies Are Better Than One
Once Lutonix succeeded in establishing the scientific basis underlying the company’s carrier molecule, the next step was to see whether the formulation would succeed in the clinic. Here again the company went to extraordinary lengths for a start-up to ensure that it could demonstrate the clinical effectiveness of the Moxy balloon. Lutonix chose to establish that this technology was effective for three different clinical applications - including both coronary and peripheral, and to do so conducted three separate, simultaneous pilot studies.

In determining which clinical areas the company would pursue first, Wahr points out that “Our initial clinical indications are those for which stents are either not
well suited or may be less effective.” These include peripheral artery disease (PAD), both the superficial femoral artery (SFA) and vessels below the knee, along with coronary in-stent restenosis and small de novo coronary lesions, as well as bifurcations.

Lutonix's decision not to directly challenge drug-eluting stents was both commercially and clinically driven. Despite the appeal of a therapy that doesn't leave a permanent implant behind, the fact is that drug-eluting stents have proven remarkably successful, even with the late-stent thrombosis issue, at treating coronary artery disease, so for Lutonix to attempt to challenge the entrenched position of DES, let alone the sales and marketing heft of the major cardiovascular players, would be a significant commercial and financial risk for a small start-up.

Besides the commercial obstacles, the clinical hurdles that Lutonix would have to overcome in attempting to gain regulatory approval for applications that compete with DES would have been equally challenging and, based on the fate of previous start-ups, what some would call a foolhardy effort. The size, complexity, duration and cost of the clinical trials currently required by the FDA to just demonstrate equivalency to drug-eluting stents have proven too daunting for even well-funded and ably managed start-ups, with now-defunct Xtent being perhaps the most notable example.

Instead, when it comes to competing with drug-eluting stents, Lutonix has chosen to follow a much more manageable “Hit ‘em where they ain’t” strategy, in the words of baseball's Wee Willie Keeler. That strategy was partly the result of the commercial and clinical realities of the DES market, but Dennis Wahr acknowledges that the decision to pursue several possible clinical applications of the drug-coated balloon was also simply an effort to maximize the chances that Lutonix would find the most promising area in which its formulation would prove effective. Wahr points out, "When we started the company, there wasn't any meaningful proof yet that our approach would really work, and if it did, what would be the best clinical indication. One of the reasons why we did coronary and peripheral trials right out of the box was as a hedge against what would happen if the balloon worked in one application but not the other.”

In addition to the potential clinical benefits, this multi-focused strategy was also designed to help with the company's future financing efforts. Given how little was known about the safety and effectiveness of drug-coated balloons when Lutonix was launched, the company's cautious, "strength in numbers” strategy when it came to clinical trials, rather than looking for that one, killer app for drug-coated balloons, was designed to make the company more attractive to investors through demonstrating its technology could have a variety of potential applications. "Since it wasn't yet known where drug-coated balloons would work best, we decided not to try to prove that this technology was going to become the definitive therapy for any specific clinical indication," Dennis Wahr explains. "Instead, I wanted to run three very different, but complementary trials so that our first-in-man trials would create a synergistic matrix that, viewed as a whole, would clearly demonstrate that this technology works. That was really the bar I wanted to get over because I knew that raising our Series C round was going to take compelling clinical evidence.”

The three areas that Lutonix addressed in these studies were coronary in-stent restenosis with the Pervideo I study, peripheral disease in the SFA with the Levant I trial, and coronary de novo lesions in the De Novo study. The De Novo study involved the use of the Moxy balloon together with a bare-metal stent. Wahr says this trial was a direct result of questions from the FDA as to how the company’s balloon would work in conjunction with a stent. According to Wahr,
Knowing the DCBs would occasionally be used with a bare-metal stent, the agency asked us right out of the box whether we knew if our device would be safe if a stent was implanted following use of the balloon. They were specifically interested in knowing whether the vessel would heal properly and whether there was a risk of thrombosis." The trial demonstrated a clear ability to inhibit restenosis, measured by a late lumen loss of 0.43 millimeters, while also reporting a good stent healing response and no reported thrombosis.

The Levant I trial was Lutonix’s first-in-man peripheral study, representing the primary market the company will be pursuing with the Moxy balloon. The study was a 101 patient, prospective, multi-center, randomized controlled trial comparing the Lutonix balloon with standard balloon angioplasty for treatment of SFA disease with and without stenting. Here again the study met its primary endpoint, which was late lumen loss at six months of 0.46 millimeters, basically duplicating the results of previous DCB studies.

Lutonix structured the Levant I trial knowing that this data would go to the FDA in support of the company’s IDE request to launch its pivotal trial. As a result, this was a heavily monitored study, using independent core labs for angiographic review. “We also felt that we had to randomize our peripheral trial because there’s not nearly as much historical data for the peripherals as there are for the coronaries, and the trials that have been done in the leg are all so different that it’s hard to determine what to pick for a control group,” Wahr notes.

The result was that Lutonix recently received the first IDE approval for a drug-coated balloon pivotal study in the US. The company has just started enrolling patients for the Levant II randomized trial, which will compare the Moxy balloon with traditional angioplasty in SFA lesions in 476 patients at 55 US and European sites. The primary endpoint is composite safety and efficacy at 12 months with five-year patient follow-up. Wahr estimates that patient enrollment will take 12 to 18 months to complete. Since patient follow-up is for one year, that means the earliest data from the study will be released is likely to be early in 2014.

In-stent coronary restenosis is the other potential application that Lutonix studied, and in this area the company employed a registry, rather than a randomized trial. According to Wahr, “In the coronaries we felt comfortable using a registry because many randomized trials have been done in the coronary anatomy using the same late lumen loss endpoint, which has become the gold standard, so we didn’t feel we needed to invest the money on randomization for the first-in-man trial.” Like the other two studies, the Pervideo I ISR study produced positive results, with the Moxy device demonstrating a clear biologic effect against in-stent restenosis through the ability to inhibit neointimal hyperplasia with no reported thrombosis on a shortened DAPT regimen.

**A Contrarian’s View**

The success of all three of Lutonix’s first-in-man trials marked the completion of the second leg of the company’s milestone-driven financing strategy. As noted, Wahr had used the Series A funding to identify an optimal formulation through a combination of benchtop research and animal studies, and to establish the underlying scientific basis for the Moxy technology. With that evidence in hand, in October of 2008, the company closed a $25 million Series B financing led by Versant Ventures, while also adding Delphi Ventures, which carried Lutonix through the FIM trials. [See Deal] The timing of the Series B round was fortuitous in light of what was happening to the global economy. Dennis Wahr recalls, “We had our term sheets in hand just before the economy crashed.
Fortunately, it was a very competitive round with a number of interested 
investors because otherwise we were worried that investors would back out if 
we didn't have that level of interest."

Armed with the FIM data, Lutonix went on the road last summer to raise the 
funding to get the company through the Levant II pivotal trial. "It was a very bad 
environment to raise money in," Dennis Wahr notes, "but we did a small road 
show and wound up with five term sheets." The Series C round included all of 
the existing insiders, along with new investors Warburg Pincus and The Vertical 
Group. [See Deal]

Wahr estimates that the C round will carry the company for upwards of two 
years, enough to complete the US pivotal trial and begin to prepare Lutonix for 
commercialization. Indeed, one of the reasons Wahr hired Shawn McCormick 
and Leslie Trigg was to transition Lutonix from a clinical- to a commercial-stage 
company.

One of the major challenges of developing any drug/device combination product 
is the cost of that development process, a large piece of which is the extended, 
complex clinical trials required for regulatory approval. Some industry experts 
estimate that, in the current regulatory environment, developing a new drug-
eluting stent can cost upwards of $500 million over a 10-year period. Lutonix 
does not believe that developing a drug-coated balloon will be nearly as costly if 
done efficiently. One obvious difference, of course, is that using a balloon is 
less complex than developing a stent, and it also does not entail a permanent 
implant, thereby simplifying the clinical trials process. The company estimates 
its total development costs through to cash-flow break-even will be around $125 
million. In terms of the company's financing goals, Dennis Wahr notes, "I want 
to come out of the next round of financing with all of the remaining cash 
necessary to take the company to cash-flow break-even sitting around the 
table."

Versant's Kevin Wasserstein points out that "in order to pursue a peripheral 
application for its balloon in the US, Lutonix is running a 476-patient randomized 
study, whereas if the company was developing a drug-eluting stent, it would be 
looking at a 1,500-plus patient study." He adds that "picking the peripheral path 
first is both logical and practical since that is where most clinicians believe that 
drug-eluting balloons are going to cut their teeth, as opposed to the coronaries."

Many industry executives and venture investors believe that the high clinical 
trials bar for DES is largely responsible for preventing start-ups from 
successfully competing in this market, with a company like Xtent, as noted, 
cited as the most frequent example of an innovative technology that did not 
make it to the market due to these onerous regulatory standards. As Kevin 
Wasserstein notes, "Because drug-eluting stents have largely worked so well, a 
product that is going to compete head-to-head with a DES would need very 
sizeable patient populations in clinical studies to demonstrate a clinically 
significant benefit."

Dennis Wahr, however, may be among the minority in the device start-up 
community who take a contrarian view on the FDA's requirements both for 
preclinical and clinical studies of these products. According to Wahr, "On the 
preclinical side, the FDA is absolutely correct in having the same high bar for 
drug-coated balloons that they have for drug-eluting stents." In his view, there is 
no way to evaluate product safety for any drug/device combination product 
without looking at the animal studies. "You have to look at the histopathology 
and the pharmacokinetics whether the drug is coming off a stent, a balloon or a 
pill," he insists.
In terms of the clinical trial size now being required, Wahr contends that here, too, the FDA's demands are not excessive. "The size of any trial is set by how well the control arm does, and the reason why coronary trials are so big is because if the control arm involves a DES, those patients typically do very well," he explains, echoing Wasserstein’s comments. "If the current standard of care, as reflected in the control arm, isn't very good, then a company won't have to enroll nearly as many patients in order to demonstrate superiority." That is why Lutonix only needs to randomize 476 subjects for its peripheral trial against standard angioplasty balloons, which have not been proven nearly as effective as drug-eluting stents have been in the coronaries.

**Smaller Risk, Big Opportunity**

Lutonix's strategy of not going head-to-head against drug-eluting stents and instead pursuing smaller niche markets not currently well served by DES will significantly reduce the company's commercial risk while still providing significant opportunity. Indeed, initially pursuing PMA approval for the Moxy balloon for the peripheral vascular market, based largely on the Levant II trial results, will potentially provide the company with access to a $1.5 billion global opportunity. Lutonix estimates that 80% of that will come from the SFA market, where the dominant therapies currently are stents, balloon angioplasty and atherectomy, but the outcomes are less than ideal with high restenosis rates, anatomic flex issues, and problems with stent fractures. The remaining 20% of the peripheral market is in below-the-knee arteries, where angioplasty is currently the treatment of choice, and the outcomes tend to be inconsistent and unpredictable with high restenosis rates. (See Exhibit 1.)

**Exhibit 1**


<table>
<thead>
<tr>
<th></th>
<th>US</th>
<th>Europe</th>
<th>Asia &amp; ROW</th>
<th>Worldwide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SFA-Popliteal</strong></td>
<td>218,750</td>
<td>232,000</td>
<td>310,000</td>
<td>860,750</td>
</tr>
<tr>
<td><strong>Below-the-Knee</strong></td>
<td>74,950</td>
<td>75,000</td>
<td>72,000</td>
<td>221,990</td>
</tr>
<tr>
<td><strong>Total Leg Procedures</strong></td>
<td>456,740</td>
<td>306,604</td>
<td>382,000</td>
<td>1,082,740</td>
</tr>
</tbody>
</table>

**Source:** Lutonix

According to Kevin Wasserstein, another benefit of drug-coated balloons compared with drug-eluting stents is that, while both have the higher up-front costs required to develop a combination product, Lutonix and other balloon companies have the advantage of much lower market development costs. "As soon as Lutonix is able to show the clinical impact of its device in a particular patient population, the market adoption profile of this company relative to other device companies could be unprecedented," he predicts. "Lutonix will be innovating a brand new product category, yet the device requires very little market development since doctors already know how to deliver balloons."

Indeed, because interventionalists have long been familiar with the use of angioplasty balloons, Lutonix's product does not involve a major learning curve or require significant in-service training or use of cadaveric models. The procedure is basically the same as what clinicians have been performing for more than 30 years. "It's just like delivering a stent," Dennis Wahr explains, adding, "We prefer that the doctor pre-dilate the vessel because we want to ensure a clear channel for the delivery of the drug-coated balloon."

Although there isn't the concern about risks like edge effect that result from improper stent placement, Dennis Wahr points out, however, that the procedure
still requires "disciplining the doctor to take the same kind of mentality with drug-coated balloons that they use with stents because if they don't choose the right diameter or put the Moxy up in the right spot, they won't treat the right spot in an optimal way." Lutonix is looking to avoid what Wahr calls the "plain old balloon angioplasty mentality" where if a physician inflates a balloon in the wrong spot, he routinely pulls it back, and relocates and re-inflates it.

"At the end of the day, the beauty of this technology is its simplicity," Leslie Trigg notes. "This will be a tool that physicians will quickly be quite comfortable with." As a result, Kevin Wasserstein expects that "the adoption profile in this category could be very rapid, which is unheard of with an innovative technology like this. There aren't many device markets where a technology can be both disruptive and have such a rapid market adoption profile."

As the only company with an approved IDE, Lutonix looks to be well ahead of any potential competitors in the race to bring a drug-coated balloon to the US market. Medrad Inc., a division of Bayer AG's Bayer HealthCare Pharmaceuticals AG, is the only other company that appears to have first-in-man peripheral data, having received CE mark approval earlier this year of its Cotavance drug-eluting balloon.

In Europe, the DCB market is much more competitive in the coronary, rather than the peripheral market. There are nearly a dozen companies with CE mark-approved coronary devices, while Invatec SPA, a division of Medtronic Inc., and Medrad are the only companies with approved peripheral products. (See Exhibit 2.) Lutonix is well-positioned to enter the European market, having received CE Mark approval of the Moxy balloon for both peripheral and coronary applications in June of this year. The company would seem to be a logical candidate to join the growing number of US device companies that are introducing products initially in Europe to begin generating revenue during this time of uncertainty with the FDA regulatory process. Dennis Wahr is reluctant to discuss the specifics of Lutonix's sales and marketing plans in Europe other than to say, "We definitely see ourselves commercializing outside the US well in advance of US approval."

**Exhibit 2**

**Selected Private Drug-Eluting Balloon Companies**

<table>
<thead>
<tr>
<th>COMPANY (LOCATION)</th>
<th>PRODUCTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aachen Resonance (Germany)</td>
<td>Ektar balloon uses no excipient, instead has two layers of paclitaxel. Process allows for coating the balloon while it is inflated. Drug adherence in the dry state minimizes drug loss when the balloon is folded.</td>
</tr>
<tr>
<td>Acrostak International (Switzerland)</td>
<td>Developing Genie, which is not a balloon but a liquid drug delivery catheter for addressing restenosis with paclitaxel.</td>
</tr>
<tr>
<td>AngioScore (US)</td>
<td>Drug-eluting balloon in development will take advantage of scoring features of core product AngioScript, balloon with nitinol scoring scaffold, to enhance drug penetration in artery wall while minimizing tissue trauma.</td>
</tr>
<tr>
<td>Avital Vascular (Germany)</td>
<td>DDB for coronary applications uses surface modification technology that increases the homogeneity and efficiency of drug application and design protects the drug to eliminate washout (according to company press release).</td>
</tr>
<tr>
<td>Blue Medical Devices (Netherlands)</td>
<td>Protégé use paclitaxel formulated in a hydrophilic coating and protects it within folded balloon wings. The coating only releases when the balloon is inflated.</td>
</tr>
<tr>
<td>Concept Medical (India and US)</td>
<td>MarkTouch balloon works on Fick's law of diffusion and the concentration gradient of tissue. The company converts the drug particles from microns to nano-sized particles and places them into a coating composed of two excipients.</td>
</tr>
<tr>
<td>Conic Vascular Technology (Switzerland and Spain)</td>
<td>Conical balloon shape designed to conform to the shape of the artery and minimize trauma; narrowing of distal end provides for enhanced tractability and crossing, particularly in bifurcations.</td>
</tr>
<tr>
<td>CV Ingenuity (US)</td>
<td>Undisclosed paclitaxel-eluting balloon.</td>
</tr>
<tr>
<td>Eurocr (Germany)</td>
<td>DIOR (for coronary applications) and Feasway (for peripheral lesions) balloons have paclitaxel dissolved in shellac, an organic FDA-approved compound used widely in the cosmetics industry. The balloon is folded, further protecting the drug from washout on the way to its destination.</td>
</tr>
</tbody>
</table>
Wahr is quite comfortable with Lutonix's gradual approach of making sure that the commercial side of the business doesn't get ahead of the clinical. Many in the industry believe that is what contributed to the problems that befell drug-eluting stents, with clinicians using the devices for off-label indications, something Wahr is well aware of as a potential concern for Lutonix.

In Dennis Wahr's view, however, US adoption patterns for DCBs will be different than those in Europe. According to Wahr, "Drug-coated balloons will first gain a foothold for the areas that are not well served by stents, so that means starting in the peripherals - SFA and below the knee. After that, you may see adjunctive use with other therapies such as bare-metal stents or atherectomy in the peripherals."

Because of US regulatory issues, Wahr believes coronary applications of DCBs won't occur until later. "Coronary use will begin with ISR and maybe small coronary vessels and bifurcation side branch lesions," he suggests. "Eventually, if the data from large-scale studies are excellent, drug-coated balloons might start to compete with stents in the coronaries, but that's going to take a long time."

For as familiar as interventional cardiologists are with angioplasty balloons, Dennis Wahr acknowledges that perhaps the most substantial obstacle to adoption Lutonix will face is the significant skepticism that remains among the clinical community about the effectiveness of drug-coated balloons. "Physicians are skeptical that our data can be that good in the absence of a stent, but that is understandable because the success of drug-eluting stents is deeply embedded and it's hard to change that mind-set," Wahr notes. "Now all of a sudden we come along with a drug on a balloon and say they'll get a great result and it seems too good to be true. That is why we are focusing so much on getting the science and the data right, so we can prove to them that it is true. That is the only way we can change their minds."

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