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EQT CONTINUES DEVICE EXIT

SCA gets deeper into health care with proposed $2.9 billion BSN buy

By Omar Ford, Staff Writer

Svenska Cellulosa AB (SCA) has entered into an agreement to acquire Luxembourg, Germany-based BSN Medical Ltd. for about $2.9 billion. The Stockholm, Sweden-based company is acquiring BSN from private equity firm EQT, and the transaction is expected to close during 2Q17. The acquisition will give SCA access to the wound care market and will be fully debt funded.

The BSN Medical buy comes on the heels of SCA revealing it would split into two distinct companies – a global hygiene firm and forest products company. SCA said that a distribution and listing of its hygiene business will create more shareholder value and incur a relatively low transactional risk with low transaction costs. Its forest products unit will retain the SCA name.

See BSN, page 3

REGULATORY

Despite Cures Act, regenerative med faces uncertainty

By Mark McCarty, Regulatory Editor

The 21st Century Cures Act featured several provisions for regenerative medicine, most of which are aimed at the FDA. Gil Van Bokkelen, chairman and CEO of Athersys Inc., told *Medical Device Daily*, that payers lack experience with this branch of medical science, and thus there is some uncertainty as to how payers will view such therapies.

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REPLACES VISCOSUPPLEMENTATION

French regeneration technology for treating osteoarthritis in trial

By Bernard Banga, Staff Writer

Paris – Stemcis, a French company specializing in adipose-tissue cell engineering, is conducting a clinical trial in Spain of its adipose stem cell-based technology for treating osteoarthritis. This treatment could achieve a technological leap forward

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MAINTENANCE, MAN

Clovis handily adds tool in ovarian therapy, will show more data soon

By Randy Osborne, Staff Writer

The treatment vs. maintenance conundrum raised by Clovis Oncology Inc.'s accelerated approval of Rubraca (rucaparib) therapy for advanced ovarian cancer is nothing new, Robert Coleman, one of the principal investigators in the ARIEL trial program, told *Medical Device*

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OPENING DOORS ON XELERATOR

Israel's Medx Ventures seeks earliest-stage med-tech innovations

By Merrill Weber, Contributing Writer

JERUSALEM – At a time when medical device investors typically focus on technology development, one Israeli group is implementing a strategy to search out and identify medical technologies at their earliest stages and push them forward.

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CARDIOLOGY EXTRA

Production Editor Andrea Gonzalez on one of med-tech's key sectors

Read this week's Tuesday Special

APPOINTMENTS AND ADVANCEMENTS

Bloomington, Minn.-based **Healthpartners Institute** will welcome a new President in 2017. Nico Pronk, will assume the role of leading the research and education institution. Pronk is currently a senior research investigator at the Institute and chief science officer at Healthpartners. He has been a researcher with the Institute since 1994.

Misonix Inc., of Famingdale, N.Y., reported the appointment of Stavros Vizirgianakis as the company's president and CEO. Vizirgianakis has served as interim CEO since Sept. 2, 2016, and has served as a member of the Misonix board since May 2013. Separately, the company reported the resignation of T. Guy Minetti from the board after leading the board process to recruit Vizirgianakis to accept the CEO role. Vizirgianakis was managing director of Ascendis Medical from January 2014 to July 2016. On Oct. 25, 2016, Misonix reported that Vizirgianakis invested $4 million through the purchase from the company of 761,469 shares of Misonix common stock in a private placement at a price of $5.253 per share. Upon closing of the acquisition of these shares, Vizirgianakis became the company's largest shareholder. Misonix develops therapeutic ultrasonic medical devices.

Penumbra Inc., of Alameda, Calif., reported that Thomas Wilder has been appointed to its board, effective Jan. 13, 2017. Wilder will serve on the board for a term expiring at Penumbra's 2019 annual meeting of stockholders. Wilder most recently led Sequent Medical Inc., a company dedicated to the development of catheter-based neurovascular technologies, as its CEO for the past six years. Wilder currently serves on the board of Benvenue Medical Inc. and Endologix Inc. In connection with Wilder's appointment, Walter Wang (Wang Ventures) is stepping down from the board of Penumbra, where he serves on the Audit and Executive Committees and as chair of the Compensation Committee. His resignation is effective Jan. 13, 2017. With the concurrent arrival and departure of these directors, the Penumbra board will be comprised of five directors, three of whom are independent. Wilder will serve as the chair of the Compensation Committee and as a member of the Audit, Executive and Nominating and Corporate Governance Committees.

Portable Genomics Inc., of San Diego, reported the appointment of Aarush Manchanda as a new investor and member to its board. He is board certified in internal medicine, cardiovascular disease, nuclear cardiology, cardiac computed tomography and echocardiography. He currently works as a staff cardiologist at Cedar City Heart Clinic and as the medical director of cardiovascular services at Cedar City Hospital in Cedar City, Utah.

PRODUCT BRIEFS

Biotrace Medical Inc., based in San Carlos, Calif., reported the first commercial use of the company's Tempo Temporary Pacing Lead since FDA 510(k) clearance in October of this year. The first cases involved patients undergoing transcatheter aortic valve replacement (TAVR) procedures and were performed by James Harkness and Brian K. Whisenant at Intermountain Medical Center in Salt Lake City, Utah, and Susheel Kodali at Columbia University Medical Center/New York Presbyterian Hospital. Biotrace Medical's Tempo Lead is for use in procedures in which temporary pacing is indicated, including TAVR and electrophysiology procedures. The lead is designed for secure and stable cardiac pacing with the goal of reducing complications and allowing patients to ambulate sooner after procedures.

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BUSINESS OFFICE

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BSN

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"This is another step in the journey of the hygiene part of SCA," said Magnus Groth, president and CEO of SCA, during a conference call discussing the BSN acquisition. "We've been looking at the medical solutions market ever since 2011 as an opportunity for future growth."

BSN is home to such wound care product lines as Leukoplast, Cutimed, Jobst, Delta Cast, Delta Lite and Actimove, which are long established brand leaders in key markets, Groth said. BSN has a strong go-to-market and supply chain with sales in more than 140 countries and production in 11 countries. It also has about 6,000 employees and competes directly against companies like Berkshire, U.K.-based Convatec Group plc.

"While at first sight this looks to be an unusual diversification into health care from its core hygiene business, BSN and SCA's incontinence business have complementary features, as they both use the same distribution channels and there will be opportunities for mutual cross-selling," said Adam Kindreich, an analyst with Morningstar.

Kindreich said that BSN comes with some drawbacks that he viewed as potential opportunities.

"Emerging markets account for less than 20 percent of sales, vs. 32 percent at SCA," he said. "In addition, BSN has been underperforming relative to peers with 3 percent organic sales growth, vs. 4 percent for the industry, mainly due to negative mix. Some of BSN's categories are suffering from ongoing price pressure, similar to SCA's."

BSN reported net sales for 2015 of $891 million. The reported net sales for BSN for the first nine months of 2016 amounted to $652 million.

"BSN has been a very resilient business in good times and in bad, with a steady growth in both top line and in profits," Groth said.

SCA said it expects to realize annual synergies of at least $31.2 million with full effect three years after closing. These include sales synergies from accelerated growth from cross-selling of BSN products and SCA incontinence products as well as cost synergies primarily in supply chain and administration. Restructuring costs are expected to amount to about $10.4 million and are expected to be incurred in the first three years, following completion, SCA said.

BSN was founded 15 years ago as a joint venture by Germany's Beiersdorf and London-based Smith & Nephew plc. London's Montagu Private Equity acquired BSN in 2006 for about $1.1 billion and then sold it to EQT for $2 billion.

BSN's owner, EQT had been mulling over a sale of the company for quite some time. Earlier this month, it was reported that EQT was thinking of an initial public offering for BSN.

The sale of BSN is EQT's second exit from a health care business. In May, EQT agreed to sell Malmö, Sweden-based Atos Medical AB to Pai Europe for $884 million. EQT bought the voice box prosthesis company in 2011 from Nordic Capital, also a private equity firm. //

OTHER NEWS TO NOTE

Cancer Targeted Technology LLC (CTT), of Seattle, said the National Cancer Institute exercised the $2 million phase II option of a Small Business Innovation Research (SBIR) phase I/II fast-track $2.3 million contract to develop a new agent to treat metastatic prostate cancer. The contract develops a promising unique radiotherapeutic drug, CTT1403, that targets Prostate-Specific Membrane Antigen (PSMA). PSMA is over-expressed on prostate cancer and expression increases as the cancer metastasizes and becomes castrate-resistant. CTT's phosphoramidate-based agents, bind irreversibly to PSMA and unlike other agents targeting PSMA, this distinctive mode of binding enhances uptake and internalization by tumor cells leading to increased accumulation of the therapeutic payload and improved efficacy.

Lensar Inc., of Orlando, Fla., reported filing of a Chapter 11 bankruptcy petition on Dec. 19 to reduce its debt, strengthen its balance sheet and strengthen its platform for future growth. The filing was made with support from Incline Village-based, Nev. **Pdl Biopharma Inc.**, Lensar's senior secured lender.

Lombard Medical Inc., of Oxfordshire, U.K., and **Microport Scientific Corp.**, of Shanghai, reported a strategic partnership and a significant infusion of capital into Lombard Medical by Microport. Microport has invested $15 million in a combination of Lombard Medical common stock and convertible debt. Microport purchased $5 million in common stock at 62 cents per share representing a 29 percent ownership stake in Lombard Medical based on common stock currently outstanding. This partnership will allow Lombard Medical to accelerate commercialization in key global markets with its two key products: Aorfix and Altura. The agreement provides Microport the exclusive marketing rights for Lombard Medical's Aorfix and Altura AAA stent graft product lines in China, as well as the right to a technology license to manufacture the products for the China market. Lombard Medical and Microport will also enter into a component supply manufacturing agreement whereby Microport will manufacture in its facilities in Shanghai certain components for the Aorfix and Altura product lines. Lastly, Microport will also have exclusive marketing rights for both Altura and Aorfix in Brazil.

McKesson Health Solutions LLC (MHS), of Newton, Mass., said the **Centers for Medicare & Medicaid Services** will continue its long-term use of Interqual Criteria for Medicare services auditing programs, extending a 17-year relationship with MHS. The contract, which will be administered by Baltimore-based **Ventech Solutions Inc.** on behalf of CMS, provides access across the spectrum of Interqual Criteria to help support quality oversight, utilization review, and appeals decisions.

Regenerative

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The Cures Act, as the legislation has come to be known, features regenerative medicine in at least four sections, including one section calling on the FDA to draft more extensive regulations and guidance pertaining to regenerative medicine. The evidence needed to establish safety and efficacy is not the same as that needed to meet Medicare's reasonable and necessary standard, but Van Bokkelen said this is not the only issue with coverage and reimbursement for regenerative medicine.

"Many people believe regenerative medicine has a greater potential" to deal with problems associated with aging than is available from conventional therapeutic approaches, Van Bokkelen said. He pointed out that the U.S. is not the only nation with a post-World War II up-tick in fertility, and that consequently a number of nations have a strong interest in the potential for regenerative medicine to revolutionize treatment of many diseases among their older citizens.

Nonetheless, some members of the biotech industry may be a bit behind their brethren in the device industry in terms of making a case to payers. One instance of this might be found in the discussion of high-cost therapies for diseases such as hepatitis, but the costlier cancer therapies might also fall into this discussion. "They could have educated third-party payers more effectively than they did," in some cases, Van Bokkelen remarked of drugmakers, but he pointed out that there was a strong economic argument for the hepatitis C treatments even though they that drew so much fire over the cost of treatment.

More prevalent now is the thought that the health care system as a whole has to see value in a therapeutic, and although Van Bokkelen said it is up to the sponsor to make their argument to payers, "the sponsor needs to be working with the patients and physicians" to make that case to payers as well. Despite the less-than-optimal showing of this kind of engagement with payers, he acknowledged, "it is occurring. It's not as far-reaching as I would like," he stated, but he pointed out that several advocacy organizations have been formed that boast a variety of stakeholders, all with the intent engaging with payers as well as with the FDA.

Historically, private payers are often reluctant to get into a discussion of something that sounds expensive, but they are more open to such discussions than in the recent past, Van Bokkelen said. When asked whether he saw a serious problem should the least costly alternative (LCA) approach to spending control find its way back into the Medicare discussion, he said, "I have serious reservations about that type of philosophy."

"I always worry about too much concentrated decision-making," Van Bokkelen observed, but he asserted that the narrative regarding high-cost treatments is not particularly clarifying. He pointed out that the U.S. still fosters a hugely disproportionate share of diagnostics and therapeutics, and that the vast majority of prescriptions are filled with generics. "The last thing we want to do is dis-incentivize" innovation with policies such as LCA, he said, particularly given that medical science is "now on the cusp of a whole new phase" of medicine.

"I think there are potential coverage gap issues," Van Bokkelen said, such as the problem of developing codes for inpatient and outpatient use of therapies, but he added, "I think those things will be addressed" as the evidence accumulates.

Section 3036 of the 21st Century Cures Act also provides a definition for the term "regenerative medicine and advanced therapies," which lists cell therapy, gene therapy, gene-modified cell therapy, therapeutic tissue-engineering products, and combination products using any such therapies or products.

"Historically there is no defined term," Van Bokkelen said, stating that this was included in the legislation for the sake of clarity as much as anything else. However, he noted that some have argued that the authors of the legislation didn't go far enough in populating that list.

Section 3033 of the Act deals with accelerated review for advanced therapies using regenerative medicine, but Van Bokkelen, who chairs the board of governors at the National

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Athersys eyes ischemic stroke market

Gil Van Bokkelen, chairman and CEO of Athersys Inc., has a lot to say about regenerative medicine, but his company has something in the works to challenge some of the existing therapies for ischemic stroke. The company has won a special access protocol for the phase III study of the Multistem cell therapy product, which might move past existing approaches, such as the use of tissue plasminogen activator (tPA), in part because the company's product can be effective for a much longer window after the index event.

Plasminogen treatment typically has to take place within three to four hours in order to exert a significant therapeutic effect, roughly the same window through which mechanical means of clot removal must also be administered. Van Bokkelen told *Medical Device Daily* that Multistem can be administered to significant effect out to as many as 36 hours after the event.

Athersys reported in September that it received a special protocol assessment for the company's Master-2 study of the Multistem therapy, a study that will randomized 300 patients to a placebo-controlled study in the U.S., Canada and Europe. The study will use a modified Rankin Scale score to evaluate disability after stroke, which will be evaluated at three months, but Multistem is the subject of a trial in Japan as well. Secondary endpoints will be tracked out to one year, as will clinical outcomes such as rehospitalization, a big consideration for payers of all stripes.

– Mark McCarty, Regulatory Editor

Regenerative

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Center for Regenerative Medicine at Case Western Reserve University, said there is little reason to be concerned about whether the FDA has sufficient expertise in the related areas. "I think the FDA has a lot of talent, particularly within CBER," he said of the Center for Biologics Evaluation and Research. "In fact, having got to know the leadership team, I'd say they have a tremendous amount of knowledge and expertise."

The agency will no doubt need to hire more expertise as the science advances, and Van Bokkelen said the Cures Act gives the agency the flexibility it needs to hire more talent. He acknowledged that the hiring process at the Office of Personnel Management can be cumbersome, which he said "is something that has been recognized for some time." At times, the salary differential between the agency and industry is a sticking point as well, but he noted that the FDA has several hundred million dollars to work with, much of which can be applied to staffing. //

PRODUCT BRIEFS

Bioventrix Inc., of San Ramon, Calif., reported the first closed-chest Revivent TC Transcatheter Ventricular Enhancement System procedure in Germany since receiving CE mark certification. The Less Invasive Ventricular Enhancement, or LIVE, procedure was performed by Christian Frerker, Tobias Schmidt and Ralf Bader at Asklepios Klinik St. Georg in Hamburg, Germany. The physicians implanted two anchor pairs and achieved a left ventricular volume reduction of 24 percent, which is a significant improvement for a patient suffering from ischemic heart failure. By remodeling the LV to a more normal shape and size, the implant improves pumping efficiency, decreases wall stress and immediately reverses patient symptoms.

Cepheid Inc., of Sunnyvale, Calif., said it received clearance from the FDA for Xpert MRSA Nxg, the next generation methicillin-resistant *Staphylococcus aureus* (MRSA) infection control test from the leader in healthcare-associated infection (HAI) testing. Xpert MRSA Nxg is an accurate, on-demand, molecular test that delivers actionable results in about an hour. Xpert MRSA Nxg was developed using an extensive library of MRSA strains collected from around the world and demonstrates unprecedented strain coverage. Integral to the new test design are updated PCR primers and probes that detect both mecA and mecC strains, which reduces the frequency of false-positive results due to "empty cassette" strains. The test has been validated for use with both Eswab (Copan) and rayon swabs.

Stemcis

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in treating a pathology affecting 20 percent of the world's population.

Stemcis recently launched a comparative clinical trial of its technology and hyaluronic acid therapy (viscosupplementation). This trial involved forty patients at two hospitals in Barcelona, Spain: the rheumatology departments at Germans Trias i Pujol Hospital and Trauma Salut Clinic. Patients will be monitored for one year, with several intermediate consultations to assess their pain using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) of symptom severity in lower-limb osteoarthritis.

Stemcis is a subsidiary of Diagnostic Medical Systems, a French group valued at $29.8 million on the Euronext stock exchange (Paris). For the past three years, the company has been developing an adipose tissue stem cell-based therapeutic approach to treat osteoarthritis. Stemcis was set up in 2008 by two French cell biologists: Régis Roche and Franck Festy. It is based in Sainte-Clotilde (Réunion) and Besançon (Bourgogne-Franche-Comté region), and specializes in lipofilling for soft-tissue reconstruction and in regenerating some types of equine and canine musculoskeletal tissue.

"Since being acquired by DMS, we've been investing over $1 million a year in R&D on human adipose tissue," Roche, director of Stemcis, told *Medical Device Daily*. Stemcis' 10 cell and biotechnology engineers have developed new patented technology enabling adipose cells and stem cells to be quickly removed, purified and reinjected for osteoarthritis treatment and tissue vascularization. Stemcis' system makes it possible to handle adipose tissue in a closed circuit without external contact. This system includes a sterile cell-extraction kit comprising cannulas, tubes and syringes with specific diameters, shapes and porosity. The adipose tissue removed undergoes mechanical dissociation followed by centrifugation to obtain an adipose cell solution. This solution is high in anti-inflammatory factors (interleukin 10 [IL-10]), pigment epithelium-derived factor (PEDF), transforming growth factor beta (TGFb), and mesenchymal stem cells. The solution is reinjected into patients at the same time as their operations in order to protect and regenerate their osteoarthritic cartilage.

QUICK, INEXPENSIVE MEDICAL DEVICE

Unlike the procedures of its main competitors (Cytori Therapeutics Inc., GID Group Inc., Tissue Genesis Inc.), Stemcis has developed an entirely mechanical technique that eliminates the enzyme phase. By avoiding collagenase use, Stemcis' system can purify cells in less than 15

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Stemcis

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minutes instead of the one to two hours needed for enzyme procedures. "Our technological breakthrough has three main competitive advantages: speed, much lower cost than producing the enzyme cocktail [which represents around 75 percent of other systems' total cost] and less restrictive regulatory status. This is because our technology comes under class II medical devices, whereas drug status is imposed on biological solutions treated with collagenase," said Roche. His company expects to market its centrifugation and mechanical processing device for $4,000, while the single-use kit will cost a few hundred dollars.

The Stemcis research initially enjoyed national and European recognition via funding from the French National Research Agency and the EU. Beginning in 2012, Stemcis carried out a preclinical trial on rats, which proved that its technology is effective against osteoarthritis. "Rats treated during this trial had 50 percent fewer osteoarthritis symptoms after treatment than untreated rats," said Roche. Since 2014, this technology was administered to about forty sport horses and then tested on a dozen dogs last year. "We observed significant pain reduction, lasting slowdown of osteoarthritis development and a total absence of side effects," said Roche.

A DMS-GROUP BLOCKBUSTER

Stemcis will reveal the initial results of its clinical trial in September 2017. The company intends to rival viscosupplementation, which is currently the most commonly used technique to treat osteoarthritis. This clinical trial is giving Stemcis a chance to supplant hyaluronic acid injections, which have just been delisted as an osteoarthritis treatment in France. This reimbursed market is worth an estimated $53 million in France, while the European and North American markets are also substantial. According to various European studies, there are an estimated 70 million osteoarthritis patients without effective treatment. In the U.S., one in five people (about 1.2 billion people) live with joint pain. "When this medical device comes onto the market in two years' time, the global market could be worth more than a billion dollars. It will be a real blockbuster for our group," said Jean-Paul Ansel, CEO of the DMS Group, the parent company of Stemcis.

MANY OTHER APPLICATIONS

"For the time being, we're planning to market our medical device in Spain, France and Australia – where we've had a subsidiary for the past year – from 2018 onwards," said Roche. DMS, Stemcis' parent company, plans to quickly distribute this technology throughout the U.S. by going into partnership with a major American company producing pharmaceutical and medical supplies in the U.S. "Our medical device complements the action of hyaluronic acid and medical-grade silicone. It can also remedy slackening in some tissues and promote revascularization via stem cells' proangiogenic effects," said Ansel and Roche. These two directors intend to develop technology for injecting autologous adipose cells, including stem cells. This will be used to treat urogenital afflictions such as urinary stress incontinence (3 out of 10 women), erectile dysfunction (44 percent of men over 45 years of age and 60 percent over 65 years of age), and diabetes-related disturbance to lower-limb vascularization (3,000 amputations a year in France). Outside of Europe, Stemcis has already carried out a preclinical trial on 20 urology patients. A major clinical trial involving several dozen patients is also planned for 2017. As for erectile-dysfunction treatment, a preclinical trial modeled on the one involving rats will be starting early next year. "I'm betting on human stem cells. These solutions represent a break with conventional medicine and are at the intersection of medical technology and biotechnology," said Ansel. //

Clovis

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Daily. "When paclitaxel was found to have efficacy in delaying progression in front-line maintenance more than 10 years ago, we had the same debate, pay me now or pay me later," he said.

Shares of Boulder, Colo.-based Clovis (NASDAQ: CLVS) closed Monday at $40.48, up $3.28, or 8.8 percent, on the good news about the poly ADP-ribose polymerase (PARP) inhibitor targeting about 15 percent to 20 percent of ovarian cancer patients who have the BRCA mutation. The National Cancer Institute estimates that 22,280 women will be diagnosed with ovarian cancer in 2016 and about 14,240 will die from it in the U.S. Yet to come are data from the ARIEL3 trial with Rubraca in the maintenance setting, where competitors Astrazeneca plc, of London, and Cambridge, Mass.-based Tesaro Inc. also are testing PARP inhibitors. Astrazeneca's Lynparza (olaparib) is already approved. Tesaro has rucaparib in the works.

Piper Jaffray analyst Steven Breazzano said maintenance data ultimately will tell the tale.

"While Clovis is positioned well in the treatment setting with the early approval, we anticipate both Tesaro's niraparib and Astrazeneca's Lynparza to potentially enter the maintenance setting next year ahead of Clovis' own ARIEL3 second line-plus maintenance data," he wrote in a report Monday. "Though we are optimistic for a positive result in Clovis' maintenance trial, given our view of the similarity of PARP inhibitors and Clovis' trial design, ultimately how the dynamic between maintenance and treatment evolves, as well as differentiation between the various profiles, remains to be seen."

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Clovis

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Rubraca was originally assigned a PDUFA date of Feb. 23, 2017.

Coleman, a physician at the University of Texas MD Anderson Cancer Center in Houston, said the maintenance/treatment picture can be modeled.

"You can look at the median survivorship or progression-free survivorship, and you can look at what the impact would be in the slightly reduced patient cohort that would be potentially eligible to receive [the drug] after progression. I have not done the math yet to sort that out in my head, but it's always going to be an issue as we go forward. One of the elements that are going to play into this is the cost-effectiveness angle," he said, noting that "these patients live for a long period of time, much longer than cohorts that don't carry the mutation."

Confounding the argument is patients' exposure to other therapies, Coleman said. "It would not surprise anybody that overall survival is not changed all that much because it's a distant endpoint, and yet it's also an endpoint that could be affected by alternative therapy strategies that would take advantage of the same vulnerability. We try to use the drugs as early as possible when they're indicated [because] we lose some of the patients [who go from second to third line]. They never get exposed to the drug. One of the negatives on the maintenance side is that we don't know whether or not we're impacting the natural history directly. For some people who are developing side effects and such, it's hard to keep them on, and we don't know what the downstream effects will be from long-term exposure. People on that side of the fence will say, 'Well, we should just wait until they recur and use it as a therapy, because we can see when it's working and not working, and it's likely to work for a long period of time, and we won't unnecessarily expose patients who don't need it.' People on the maintenance side of things will say, 'Listen, we've got to use it now because that's where it's going to have the greatest impact and the side effects are manageable.' In the clinic, I'm probably going to use it both ways."

LABEL MUM ON SIDE EFFECTS, MONITORING

Coleman likened the situation to the findings of the phase II ICEBERG trials done years ago with Astrazeneca's as-yet-unapproved olaparib. The simple, three-arm experiment involved two with olaparib and one with Doxil (liposomal doxorubicin, Janssen Products LP). Researchers hoped to prove olaparib's superiority.

"They were surprised," he said. "Both of the olaparib arms performed well, better than expected relative to chemo, but so did Doxil. They didn't realize that Doxil is a direct DNA-damaging agent, and in BRCA patients, who are vulnerable to that strategy, it basically did better by twofold than expected. So the trial was considered negative, but in fact it was positive to show the effect of chemotherapy in patients whose tumors have this vulnerability."

Also cleared by the FDA for use with Rubraca was Foundationfocus CDxBRCA – the first next-generation-sequencing (NGS)-based companion diagnostic. It's marketed by Foundation Medicine Inc., of Cambridge, Mass.

In October, shares of Clovis dipped when investors looked askance at data submitted in rucaparib's new drug application and presented at the European Society for Medical Oncology congress in Copenhagen. Some fretted over a lack of response in a small number of platinum-refractory patients, as well as safety and speculation about competitive strength against other PARP inhibitors. The Clovis dataset involves a pooled analysis from 106 patients and includes those treated patients one line earlier than Lynparza, and captures somatic as well as germline BRCA mutations. The former category could mean 5 percent to 10 percent more patients as compared with the Astrazeneca drug, approved for germline. Piper's Breazzano likes the Rubraca prescribing info, too, and echoed Coleman with regard to early starts.

"With a broad third line-plus label that includes all BRCA patients and a favorable combined headline overall response rate [ORR] of 54 percent (though the details describe independent ORR assessment of 42 percent and duration of response rate of 6.7 months), we believe that in the near term Clovis is well positioned to establish market share in the ovarian cancer treatment setting, as physicians we have spoken with wish to use PARP inhibitors earlier in the treatment paradigm in patients with BRCA mutations," he wrote. "The indication statement does not discriminate platinum status, though the clinical-studies section of the prescribing info describes the variable efficacy of Rubraca in platinum-sensitive, resistant and refractory patients." He said he did "not expect any impact from [these] additional data. Notably, the label does not appear to include anything particularly concerning around monitoring or side effects. The inclusion of somatic BRCA will require physicians (particularly community-based physicians who do not routinely conduct NGS screening) to test tumor tissue, though we anticipate increased testing now that Rubraca is available." //

OTHER NEWS TO NOTE

Mdxhealth SA, of Irvine, Calif., said it has signed a distribution agreement with **Acecgt Life Science Ltd**., of Herstal, Belgium, for the Selectmdx for Prostate Cancer assay in Hong Kong and Macao, Special Administrative Regions of the People's Republic of China Under the terms of the agreement, Acecgt Group will be the exclusive distributor within the Hong Kong and Macao Special Administrative Regions. Patient samples will be sent to Mdxhealth's ISO certified clinical diagnostic laboratory in Nijmegen, Netherlands, for analysis.

Medx

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The launch of a new accelerator this month pushes that effort that much further. The group, Medx Ventures, was established in 2011 by Harel Gadot, who previously was worldwide group marketing director for Ethicon at Johnson & Johnson, overseeing global strategic marketing. Medx Ventures' strategy is to evaluate prospective portfolio companies for the quality of their management team, technology and intellectual property and then assist those companies in developing their products. This strategy seems to work.

"For five years [since the founding of Medx Ventures] no portfolio company has missed a development milestone or a budget milestone," Gadot said.

Medx Ventures – which has the gamut of expertise in R&D, finance, business development and regulatory compliance – is now taking its strategy further and expanding its scope.

Earlier this month Medx Ventures opened the doors to Israel's newest high-tech incubator, Medx Xelerator. Medx Xelerator is expected to invest in minimally invasive procedures, medical robotics, medical implants (including drug eluting implants), drug-device combinations and digital health.

The Medx Xelerator is one of 19 privately owned and operated incubators that are part of the incubator program of the Israel Innovation Authority, formerly the Office of the Chief Scientist in the Ministry of Economy of the State of Israel (OCS). Under the incubator program, the group that manages the incubator makes its own decisions regarding portfolio companies, subject to approval of the OCS. The OCS covers 85 percent of the cost of funding approved companies during their two-year term in the incubator.

The Medx Xelerator is owned by a consortium that includes Medx Ventures, the Sheba Medical Center in Israel, Boston Scientific Corporation and Intellectual Ventures, a company founded by Nathan Myrhvold, the former chief technology officer at Microsoft, and that includes Bill Gates as an active participant. The incubator began operating in September and is currently evaluating five companies. Gadot expects that the incubator will submit those companies to the OCS for approval in January.

And while the incubator is located in Israel, the entrepreneurs may come from all over the world.

Gadot said that the Medx Xelerator will originate new technologies "rather than fight with other Israeli incubators for the same IP." In his analysis, translatable ideas are found in three ways: passively, actively, and proactively. The passive approach is to wait to be approached by entrepreneurs. The active approach is to develop relationships with technology transfer offices (TTOs) and physicians with ideas. The proactive approach is to work in partnership with the physicians to develop new ideas. The Medx Xelerator will function as a "pre-seed" incubator, providing the opportunity to develop new products in collaboration with leading experts.

Intellectual Ventures, Gadot said, "is adding tons of value [in advancing the proactive approach]. TTOs in Israel are extremely interested in collaborating with them." Intellectual Ventures offers "innovation sessions" in which a network of doctors who are expert in their fields, and researchers such as Robert Langer, the David H. Koch Institute Professor at MIT, will meet to understand problems encountered by physicians in their own medical practices and then work to develop solutions to those problems.

Significantly, Gadot said that rights to solutions will belong to the physician or his institution's TTO, and that Medx will license them in the same manner as though the physicians or the TTO had presented the ideas fully formed.

"We wanted to ensure that we are working with the TTOs and the physicians in a win-win situation," Gadot said.

Gadot sits on the board of the Medx Xelerator along with representatives of Boston Scientific, Intellectual Ventures, the Sheba Medical Center, and the Corundum Open Innovation Fund, a venture capital fund backed by Japanese corporations that invests in Israel high-tech companies. He also serves as CEO and chairman of Microbot Medical Ltd., a medical device company that is developing micro-robotic devices to perform surgical procedures. That company went public (NASDAQ: MBOT) in November 2016 through a reverse merger and currently has a market capitalization of approximately $300 million.

Clearly, Gadot does not want to wait for technology but chase after it.

In addition to the incubator, Medx Ventures plans to dive into an even earlier stage of medical device development, with the establishment of a pre-incubator "X Lab" where entrepreneurial physicians and researchers will work to develop prototype devices at no cost to the entrepreneurs. If the device developed by one of these entrepreneurs turns out to be of interest to the Medx Xelerator, then new companies will be formed around the technologies and those companies will join the incubator. If those technologies are not brought into the incubator, then Medx will waive all rights to the technology. If that happens, the entrepreneurs will have no further obligation to Medx, and they will be free to take their technology anywhere they wish. "We don't know of another arrangement like that," Gadot said.

Gadot is establishing a new way to measure success for a medical device incubator.

"Success is not the number of companies you put in the incubator. Success to me looks like how many companies after the incubator will have the ability to live on their own."

"If we bring in five companies per year, and four can raise meaningful funds, find strategic partners, merge into other entities to strengthen their positions, that to me is the measure of success."

Medx has operations in Israel and in Boston. Gadot said that the company has no current plans to set up operations in Silicon Valley or elsewhere. "We need to consider Israel and the incubator as a whole," he said, and not be dependent on geographical presence to originate new ideas." //

PRODUCT BRIEFS

Cerus Corp., of Concord, Calif., gave an update on the timeline for the INTERCEPT Blood System for Red Blood Cells (RBCs) in Europe. The target timing for CE mark submission has been extended. Due to the need for additional time to complete quality control tests on the Chemistry, Manufacturing, and Control (CMC) registration lots required for regulatory submission, the company now plans to provide an update on new submission timing on its 4Q16 earnings call in early March. A new submission filing date will need to be scheduled with TŰV SŰD Product Service Gmbh. Cerus' SPARC (A Randomized Controlled Study to Evaluate Efficacy and Safety of INTERCEPT Treated Red Blood Cells in Subjects with Thalassemia Major Requiring Chronic RBC Transfusion) trial has reached its enrollment target of at least 70 evaluable patients, and the company expects that study data will be available in time to support its anticipated European product launch.

Edap Tms SA, a Lyon, France-based developer of therapeutic ultrasound products, said the results comparing Ablatherm Focal HIFU with Robotic Radical Prostatectomy have been electronically published in the *Journal of Endourology*; the study will subsequently appear in a print edition. This matched pair analysis of HIFU hemiablation vs. robotic assisted laparoscopic prostatectomy was conducted by Roland van Velthoven, head of the Urology Department at the Institut Bordet Oncology Center in Brussels, Belgium. In this study, 55 patients with unilateral localized prostate cancer were treated using Ablatherm-HIFU, and their outcomes were compared 1:1 with patients having similar clinical criteria but underwent robotic assisted laparoscopic prostatectomy. The matched pair analysis concluded that HIFU was comparable to robotic-assisted radical prostatectomy in the management of prostate cancer and showed HIFU to have significantly better functional outcomes.

Endologix Inc., of Irvine, Calif., reported that the Australian Therapeutic Goods Administration (TGA) has approved the Afx2 Bifurcated Endograft System for inclusion on the Australian Register of Therapeutic Goods. The TGA has approved the use of Afx2 for the treatment of abdominal aortic aneurysms. Afx2 reduces procedure steps for the delivery and deployment of the bifurcated endograft. The new device also facilitates percutaneous endovascular aneurysm repair, or PEVAR, by providing the lowest profile contralateral access through a 7F introducer. These improvements bring together Endologix's Activeseal technology and Duraply ePTFE graft material into an integrated new EVAR system.

Masimo Corp., of Irvine, Calif., reported FDA 510(k) clearance for the Tfa-1 Single-Patient-Use Adhesive Forehead Sensor. This single-patient-use sensor allows clinicians to monitor patients using Masimo Set Measure through Motion and Low Perfusion pulse oximetry from an alternative monitoring site, the forehead, rather than a finger. Masimo Set includes measurement of oxygen saturation, pulse rate, perfusion index (PI) and PVI, a measure of the dynamic changes in PI that occur during the respiratory cycle. Masimo Set addresses the challenges of low perfusion and motion artifact that limit conventional pulse oximetry by harnessing the power of adaptive filters to reduce measurement inaccuracy.

As promised in August, **Mylan N.V.**, of Hertfordshire, UK, launched a generic for Epipen (epinephrine injection) Auto-Injector at a cost of $300 per epinephrine injection 2-pack, which the company said is more than 50 percent lower than the price of the original Epipen 2-packs. The generic, which will reach pharmacies starting next week, has the same drug formulation and device functionality as the original. Mylan also is offering a savings card for eligible patients with commercial health insurance, providing up to $25 off the out-of-pocket cost for the authorized generic. Critics have noted that's still a far cry from the $85 price in France for a two-pack of the auto-injector and more than double the price in Canada and the U.K.

Novocure Ltd., of St. Helier, Jersey, said that the Japanese Ministry of Health, Labour and Welfare (MHLW) has approved Optune (NovoTTF-100A) – Novocure's Tumor Treating Fields (TTFields) delivery system – in the treatment of adult patients with supra-tentorial glioblastoma (GBM) following maximal safe surgical resection and radiation therapy. Novocure will prepare to submit an application for public reimbursement of Optune for newly diagnosed GBM in Japan. The MHLW's approval of Optune for the treatment of newly diagnosed GBM was supported by Novocure's phase III pivotal EF-14 trial results, which showed significant extension of both progression free and overall survival in newly diagnosed GBM patients receiving Optune with temozolomide compared to temozolomide alone. Optune is the first MHLW-approved therapy in more than a decade to demonstrate statistically significant extension of survival in newly diagnosed GBM patients.

New York-based **Pavmed Inc.** said it filed a 510(k) premarket notification submission with the FDA for its first product, the Portio Intraosseous Infusion System. Portio consists of an implantable vascular access device and insertion kit. Instead of a catheter located in a vein, it has a short extension from the device, which a physician inserts into a bone, leaving the device to reside completely beneath the skin. This allows direct access to the bone marrow. Portio can be inserted and removed near-percutaneously without requiring a surgical pocket or significant dissection and will not require confirmation of the position of the tip by X-ray or other means. Once in place, the device can be accessed by the nurse through the skin using the same techniques as existing implantable ports.

Personal Genome Diagnostics Inc. (PGDx), of Baltimore, reported the launch of its Cancerselect 125 test for pan-cancer tumor profiling. Cancerselect 125 identifies clinically actionable and functionally important sequence mutations and structural alterations across multiple cancer types. The assay incorporates PGDx technologies and bioinformatics to identify tumor specific mutations. The genes in Cancerselect 125 were selected to aid in treatment decision-making based on their biological and functional relevance and clinical actionability. They include both likely and known regions associated with drug sensitivity and acquired drug resistance.

CARDIOLOGY EXTRA

Keeping you up to date on recent developments in cardiology

By Andrea Gonzalez, Production Editor

Biological pacemaker may be a reality with pluripotent stem cells

Scientists from the McEwen Centre for Regenerative Medicine, University Health Network, have developed the first functional pacemaker cells from human stem cells, paving the way for alternate, biological pacemaker therapy. Their findings, published online in *Nature Biotechnology*, detail how human pluripotent stem cells can be coaxed in 21 days to develop into pacemaker cells, which regulate heart beats with electrical impulses. Learning how to generate pacemaker cells could help in understanding disorders in pacemaker cells, and provide a cell source for developing a biological pacemaker. Biological pacemakers represent a promising alternative to electronic pacemakers, overcoming such drawbacks as a lack of hormonal responsiveness and the inability to adapt to changes in heart size in pediatric patients. The researchers used a developmental-biology approach to establish a specific protocol for generating the pacemaker cells. Based on previous findings in animal models, the researchers at the McEwen Centre tested and mapped out the specific developmental pathway of how human pluripotent stem cells become pacemaker cells. This was achieved by testing different signaling molecules at different times throughout the 21 days to guide the cells towards their goal. Once the team established which signaling pathways are activated at different stages to generate the pacemaker cells, they demonstrated that the new pacemaker cells could initiate and regulate the heartbeat in rats. The researchers noted that human clinical trials to test such biological pacemakers are from five to 10 years away, and that the next step is to launch safety and reliability preclinical trials on the pacemaker cells. Meanwhile, researchers can use their new technology to make pacemaker cells from patients suffering from pacemaker dysfunction. They can then use these patient-specific cells to study the "disease in a (petri) dish" and to identify new drugs that will improve their pacemaker function. Long term, the team hopes to develop a biological pacemaker to transplant into patients who need an electronic one. If successful, the biological pacemaker holds the promise of a lifelong cure.

Surgical ablation named best option for Afib

New clinical practice guidelines have been issued by the Society of Thoracic Surgeons (STS) that include major recommendations for the use of surgical ablation when treating atrial fibrillation (Afib), the most common type of irregular heartbeat. STS believes that the practice of summarizing current scientific evidence into clinical practice guidelines and recommendations may contribute to improving surgical outcomes, as well as the quality of patient care. In this case, the literature revealed that surgical ablation as a treatment option for Afib has experienced continued development over the last 30 years, with its frequency and success steadily increasing. The guideline writing committee merged these findings into a singular consensus paper to shape practice, concluding that surgical ablation is effective in reducing Afib and improving quality of life, and so deserves a more prominent role in adult cardiac surgery. In developing these new guidelines, the authors assessed the safety of performing surgical ablation for three surgical approaches: primary open atrial operations where the left atrium is already being opened, such as mitral valve repair or replacement and/or tricuspid valve repair; primary closed atrial operations when the left atrium would not otherwise be open, such as coronary artery bypass grafting (CABG) and/or aortic valve replacement (AVR) operations; and standalone operations when the only goal is to perform surgical ablation to treat Afib. The new clinical practice guidelines offer evidence-based recommendations that include: Surgical ablation for Afib at the time of concomitant mitral operations to restore cardiac rhythm; surgical ablation for Afib at the time of concomitant isolated AVR, isolated CABG and AVR+CABG operations to restore cardiac rhythm; and surgical ablation as a primary standalone procedure to restore cardiac rhythm for symptomatic Afib that is resistant to medication or catheter ablation. The authors also recommend a multidisciplinary heart team assessment, treatment planning, and long-term follow-up in order to optimize patient outcomes in the treatment of Afib.

Smartphone apps: a reliable method for capturing cardiovascular data

Widespread ownership of smartphones around the world could potentially transform cardiovascular research by providing rapid, large-scale and real-time measurement of individuals' physical activity. In a study published online by *JAMA Cardiology*, Stanford University School of Medicine researchers assessed the feasibility of measuring physical activity, fitness and sleep from smartphones to gain insight into activity patterns associated with life satisfaction and self-reported disease. In March 2015, Stanford researchers launched a free iPhone app – Myheart Counts – which gave users the ability to participate in a first-of-its-kind cardiovascular research study. The app uses Apple's Researchkit framework, which gives potential users a simple way to consent to participate, measure daily activities, complete tasks and answer surveys through their iPhone. Within six months of the app's launch, researchers had enrolled 47,109 participants from all 50 states. heir median age was 36 years, and 82 percent were male. Within weeks,

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researchers were able to collect data from 4,990 participants who completed a six-minute walk fitness test using the phone's built-in motion sensors, a number several times larger than the largest study previously published, the researchers said. In most of the prior clinical studies, researchers have relied on participants to estimate the time spent on physical activity in the preceding days. And people have been consistently shown to overestimate their activity levels, the study noted. Users who consented to participate in the Myheart Counts study were asked to keep their phone with them as much as possible. They were also asked to provide some basic health information – such as age, weight, blood pressure, cholesterol levels and risk factors – all of which was kept confidential. This enabled the app to provide participants with feedback on their chances of developing heart disease. Participants were also asked to complete occasional surveys on such topics as diet, well-being, risk perception, work-related and leisure-time physical activity, sleep and cardiovascular health status. Results showed that among groups of subjects with similar activity levels, those who were active throughout the day rather than in a single, relatively short interval reported better levels of cardiovascular health with lower rates of chest pain, heart attacks and atrial fibrillation. This aligns with prior findings that link prolonged periods of uninterrupted, sedentary time with increased risk for metabolic syndrome and diabetes, the study said. Results also confirmed what was already generally known: that participants were not accurate at estimating their actual activity levels. Researchers are working on an Android version of the Myheart Counts app to broaden the reach of the ongoing study, as well as an updated version of the app that will include more motivational feedback to the users about how to improve their heart health.

TEE imaging may improve outcomes for children with congenital heart disease

Using cardiac imaging during heart surgery can detect serious residual holes in the heart that may occur when surgeons repair a child's heart defect, and it offers surgeons the opportunity to close those holes during the same operation. Pediatric cardiology experts say using this tool, called transesophageal echocardiography (TEE), during surgery may improve outcomes for children with congenital heart disease. The study team published the research in the September 2016 issue of the *Journal of Thoracic and Cardiovascular Surgery*. The scientists reported on the use of intraoperative TEE to identify intramural ventricular septal defects (VSDs) – holes in the wall between two heart chambers. They performed a retrospective study of 337 children, mostly infants, who underwent surgery at the Children's Hospital of Philadelphia for conotruncal defects from 2006 to 2013. The study was the first to assess the accuracy of TEE in identifying intramural VSDs. The study team compared intraoperative TEE, which was performed during surgery, to another imaging tool, transthoracic echocardiography (TTE), done after surgery. Of the 337 surgical patients, 34 had intramural VSDs. Of those 34, both TTE and TEE identified 19 VSDs, while 15 were identified by TTE only. That data showed that TEE had modest sensitivity (56 percent), but high specificity (100 percent) in identifying intramural VSDs. The authors note that "the modest sensitivity suggests that many intramural defects are not detected in the operating room." However, they add, intraoperative TEE was able to identify most of the intramural defects requiring reintervention.

Graphene may be a new window into electrical signaling in heart, nerve cells

A Berkeley-Stanford team has enlisted the properties of graphene, a one-atom-thick layer of carbon, to function like the film of an incredibly sensitive camera system in visually mapping tiny electric fields in a liquid. Researchers hope the new method will allow more extensive and precise imaging of the electrical signaling networks in our hearts and brains. In the latest study, researchers first used infrared light produced at Berkeley Lab's Advanced Light Source to understand the effects of an electric field on graphene's absorption of infrared light. In the experiment, they aimed an infrared laser through a prism to a thin layer called a waveguide. The waveguide was designed to precisely match graphene's light-absorbing properties so that all of the light was absorbed along the graphene layer in the absence of an electric field. Researchers then fired tiny electrical pulses in a liquid solution above the graphene layer that very slightly disrupted the graphene layer's light absorption, allowing some light to escape in a way that carried a precise signature of the electrical field. Researchers captured a sequence of images of this escaping light in thousandths-of-a-second intervals, and these images provided a direct visualization of the electrical field's strength and location along the surface of the graphene. The new imaging platform – dubbed CAGE for "Critically coupled waveguide-Amplified Graphene Electric field imaging device" – proved sensitive to voltages of a few microvolts (millionths of a volt). This will make it ultrasensitive to the electric fields between cells in networks of heart cells and nerve cells, which can range from tens of microvolts to a few millivolts (thousandths of a volt). Researchers found that they could pinpoint an electric field's location along the graphene sheet's surface down to tens of microns (millionths of a meter), and capture its fading strength in a sequence of time steps separated by as few as five milliseconds, or thousandths of a second. In one sequence, researchers detailed the position and dissipation, or fade, of a local electric field generated by a 10-thousandths-of-a-volt pulse over a period of about 240 milliseconds, with sensitivity down to about 100 millionths-of-a-volt.