BioWorld MedTech

Clarivate Analytics

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January 30, 2018
Volume 22, No. 20

Noninvasive vagus nerve therapy

Electrocore snags FDA clearance of VNS therapy for acute migraine pain

By Katie Pfaff, Staff Writer

Electrocore LLC won 510(k) clearance from the U.S. FDA for its noninvasive vagus nerve stimulation (VNS) device, Gammacore, to alleviate acute pain from migraine in adults. The expanded label was approved after Gammacore received clearance for episodic cluster headache in adults in early 2017. The handheld prescription device is applied to the neck to stimulate the vagus nerve through the skin, and was backed by its recent PRESTO study.

See Electrocore, page 3

Inside

Calcivis device gives dentists new tool to fight tooth decay

By Nuala Moran, Staff Writer

A method of detecting the first stirrings of tooth decay before it can be diagnosed by visual inspection is encapsulated in a handheld, instant readout device to be launched in the U.K. in February.

The device, developed by Edinburgh-based startup Calcivis Ltd., relies on a photoprotein that

See Calcivis, page 4

Multiwave Innovation tests new generation of antennas for use with MRI brain imaging

By Bernard Banga, Staff Writer

PARIS – Multiwave Innovation SAS is currently testing the performances of a new ultra-high field MRI antenna for 7 Tesla MRI scanners at the Biomedical Imaging Institute of the Atomic Energy Commission (CEA Neuropsin) in Saclay, France.

See Multiwave Innovation, page 6

New long-acting approach to malaria prophylaxis developed

By John Fox, Staff Writer

In a new study, researchers at the U.K.'s University of Liverpool and The Johns Hopkins University School of Medicine in Baltimore have jointly developed a new long-acting nanomedicine-based delivery system for preventing malaria.

Malaria represents a significant burden of disease, with the most deadly form, *Plasmodium*

See Malaria, page 8

Attorney says totality of evidence standard is 'deeply problematic'

By Mark McCarty, Regulatory Editor

The U.S. FDA's intended use rule may be in regulatory limbo, but it and other commercial speech issues hang over stakeholders with disquieting effect. Marian Lee, a partner at the D.C. office of Gibson, Dunn & Crutcher, told

See Intended use, page 5

EMA unveils its temporary home in Amsterdam

By Cormac Sheridan, Staff Writer

DUBLIN – With its future headquarters in Amsterdam not due to be ready until November 2019, the EMA unveiled the temporary building it will start to transition to from Jan. 1, 2019, during a press briefing in Amsterdam Monday. The interim premises, the Spark Building, based in the Sloterdijk area northwest of Amsterdam's center, offers just half of the space of its present headquarters in the Canary Wharf district in east London.

It will be large enough, just about, to enable to the agency to conduct its business. "We have enough [space]. It's a less comfortable solution, but it's

See EMA, page 7

Appointments and advancements

Bionik Laboratories Corp., a Toronto-based robotics company that provides rehabilitation and assistance to individuals with neurological and mobility impairments, appointed Andre Auberton-Herve as chairman of its board. Auberton-Herve will replace Peter Bloch, who has resigned from his role as chairman, effective Jan. 24, 2018. Bloch will remain as a director. Auberton-Herve is the founder of 4A Consulting & Engineering, which provides strategic advice and consulting services with respect to renewable energy and digital innovation; he has served as its president and CEO since its founding in July 2015.

Irvine, Calif.-based **Endologix Inc.**, focused on treatments for aortic disorders, appointed Greg Morrow as its chief marketing officer, effective immediately. Most recently, Morrow led the coronary division and marketing function for Abbott Vascular.

Mardil Medical Inc., a Minneapolis-based developer of implantable medical devices for structural heart disease, reported the appointment of Martin Madden to its board. Madden retired in 2017 from Johnson & Johnson, where he most recently served as vice president of research and development and vice president of medical device R&D transformation.

Regulatory front

The U.S. **FDA** said the regulatory review period for the Sapien 3 device by **Edwards Lifesciences Corp.** of Irvine, Calif., was 1,736 days, nearly 1,560 of which took place during the testing phase. Both the agency and the sponsor have declared June 17, 2015, as the approval date, and Edwards is seeking 250 days of patent term extension for the Sapien 3. Interested parties have until March 31, 2018, to dispute the regulatory dates and until July 29, 2018, to dispute whether the patent holder acted with due diligence during the regulatory review period.

Abbott of Abbott Park, Ill., seeks 1,026 days of patent term extension for the company's heart failure monitoring system, the Cardiomems, which Abbott acquired in its acquisition of St. Jude Medical. The FDA said the regulatory review period for the device was 2,786 days, with the testing phase taking 1,525 days. Those who wish to dispute the related dates have until March 31, 2018, and anyone wishing to allege the IDE was not handled with due diligence have until July 29, 2018.

Daily M&A

Stockholm-based **Eqt Mid Market Fund** and its co-investors have entered an agreement to sell Australia-based **I-Med Radiology Network**, diagnostic imaging service provider in Australia with 204 clinics, to a company backed by the Permira funds. During Eqt Mid Market's ownership, the company has increased its fully owned clinics with more than 30 percent and the number of radiologist by more than 25 percent. I-Med has strengthened its market position in Australia and for 2017 generated revenues of almost A$700 million (US$566.75 million). The network also has invested in equipment, technology, and implemented strategies for improving customer experience. I-Med has a staff of more than 3,500 employees, including more than 300 radiologists who serve more than 30,000 referrers in the health care market in Australia. The transaction is expected to close in the first quarter of 2018. Morgan Stanley acted as financial advisor and Herbert Smith Freehills as legal advisor to Eqt.

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BioWorld MedTech

BioWorld MedTech (ISSN# 1541-0617) is published every business day by Clarivate Analytics.

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Electrocore

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The Gammacore device allows a headache patient to self-administer a mild electrical stimulation to the vagus nerve through the skin when a headache strikes, impacting the afferent nerve fibers and decreasing pain.

"With annual health care and lost productivity costs associated with migraine measured in the tens of billions of dollars in the U.S., the availability of Gammacore provides patients with a new treatment option to relieve migraine pain, while also offering the potential to alleviate some of the economic strain that arises from their condition as well," said Francis Amato, CEO, Electrocore.

About 37 million people in the U.S. are estimated to suffer from migraines, defined as debilitating recurrent unilateral or bilateral headaches that may be accompanied by visual disturbances, nausea and vomiting.

Sham-controlled study

PRESTO, which was presented at the 2017 congress of the International Headache Society, indicated Gammacore relieved acute pain from migraine better than sham, and led to freedom from pain for 30, 60 and 120 minutes in comparison to sham. The multicenter double-blind and sham-controlled randomized trial to evaluate safety, tolerability and efficacy of Gammacore noninvasive VNS (nVNS) included 243 patients with episodic migraine (120 in nVNS group, 123 with sham device). Use of nVNS resulted in greater pain freedom at treatment of the first migraine attack at 30 minutes (12.7 percent compared to 4.2 percent, p=0.012), and 60 minutes (21.0 percent vs. 10.0 percent, p=0.023). The 120-minute interval was not statistically significant (30.4 percent vs. 19.7 percent, p=0.067) though a post-hoc repeated-measures test indicated the device was better than sham through 120 minutes (odds ratio: 2.3, 95 percent CI: 1.2, 4.4, p=0.012).

Secondary endpoints of pain (mild or no pain) at 120 minutes were positive (40.8 percent vs. 27.6 percent, p=0.030) as well as the mean percent of pain reduction at 120 minutes (34.8 percent vs. 5.4 percent, p=0.004). The device was well-tolerated with low side effects, typically a temporary rash at the site of use, or allergy to nickel or ECG gel used with treatment.

De novo clearance for cluster headache

The device is not a headache prophylaxis and is not to be used with patients who have metallic implants near the neck. Also, it cannot be used in conjunction with other devices, such as a TENS unit, or mobile phones. Basking Ridge, N.J.-based Electrocore was awarded an FDA de novo clearance for Gammacore in treatment of adults with acute pain from episodic cluster headache. (See *BioWorld MedTech*, April 19, 2017.) The company filed last year for the label expansion to migraine. Gammacore is expected to be available in the U.S. for treatment of acute pain with migraine in the second quarter of this year. The device is CE marked.

> *"We have a specialty pharmacy distribution network, and they handle all the prescriptions that come in from the different headache specialists.*
>
> Francis Amato
> CEO, Electrocore LLC

$157M in funding

November brought a cash infusion for Electrocore when the company closed a series B financing for $70 million with participants including Core Ventures II, Merck & Co.'s Global Health Innovation Fund, Gakasa, American Investment Holdings LLC and Vinik Family Foundation. Earlier, the company closed a $32 million seed round and $55 million series A. (See *BioWorld MedTech*, Nov. 30, 2017.) Funding from the series B was planned to infuse efforts to expand into migraine treatment and to increase its sales force from 10 to 40 personnel.

"Our plan is to use [the financing] to help us launch more broadly into the marketplace including migraine," Amato, told *BioWorld MedTech* at the time. "We're in front of FDA, and they are looking at our therapy for the acute treatment of episodic migraine."

Financing also was aimed at expanding the company's registry program, which brings the devices to headache-focused physicians. "We have a specialty pharmacy distribution network, and they handle all the prescriptions that come in from the different headache specialists," said Amato. "There are 160 headache centers in the U.S., and we are actively working with 45 of these in a product registry, so we are making the product available to episodic cluster headache patients." The registry model leads to reimbursement as a pharmacy benefit.

Migraine patients often resort to medication, which can carry significant side effects, and unlike other VNS treatments for medical conditions, Gammacore is noninvasive and simple to use, according to the company.

VNS devices typically are implanted under the skin, including Enteromedics Inc.'s minimally invasive Vbloc vagal blocking device for obesity and Setpoint Medical's VNS device, which targets conditions associated with inflammation like rheumatoid arthritis and Crohn's disease. (See *BioWorld MedTech*, Dec. 12, 2017.) Last fall, Setpoint also began studying the device as a treatment for multiple sclerosis. A preclinical animal study determined the device could slow demyelination and increase remyelination, though human studies have not been completed. (See *BioWorld MedTech*, Oct. 31, 2017.)

Neuropace Inc. garnered $74 million in financing for its closed-loop neurostimulation, Neuropace RNS, for partial onset seizures (See *BioWorld MedTech*, Oct. 25, 2017.) ♦

Calcivis

Continued from page 1

is activated if it comes into contact with free calcium ions. An embedded camera images the transient bioluminescence that results.

The presence of free calcium ions is a symptom of demineralization, an early sign that hydroxyapatite in tooth enamel is beginning to be eroded.

"When you think about most general dentistry, it is about dealing with the consequences of demineralization, in one way or another," said Adam Christie, co-founder and CEO of Calcivis.

"At present, there are two methods of detecting demineralization: by visual inspection or by radiography. Both of these are about historic damage; with our device you can detect early signs of active disease," Christie told *BioWorld MedTech*.

Detection of active demineralization would allow teeth to be protected with sealants or fluoride varnishes, to arrest the process of decay and avoid the need for fillings. "The whole point of the device is supporting dentists in the practice of preventative dentistry," Christie said.

One teenage participant in a clinical trial of the device asked for copies of bioluminescent images of her teeth to post on Facebook. Christie suggested that illustrates how the device could provide a graphic means of reinforcing public health messages about the importance of oral hygiene and the risk of carbonated drinks causing acid erosion.

"Our system switches the light on when it detects developing caries and switches it off when [a tooth] is remineralized. In the latest clinical study, we've shown patients understand the images – especially in comparison to interpreting X-rays – and they are engaged," said Christie.

The device has European CE marking. Calcivis submitted it for FDA premarket approval in October 2017, with the FDA inspection taking place in the first three weeks of this month.

Trial design takes some work

With no existing diagnostic method against which to compare the effectiveness of Calcivis' device, the design of a trial to convince FDA required considerable discussion. "There really is nothing to draw on. There is no precedent in terms of a device and no gold standard of diagnosis against which to compare, because visual examination is not a good way to assess demineralization," Christie said.

The agreed trial design involved 110 patients attending dental practices in Scotland, whose teeth were assessed using the device. The conclusions were then checked by expert cariologists who were blinded to the diagnosis.

In the case of active lesions, there was 92 percent agreement between the conclusions drawn from the bioluminescence images and the expert visual diagnosis. In the case of sound teeth, 98 percent agreement. With no published clinical data to vouch for the accuracy of visual inspection, FDA had set a 70 percent correlation as the target that Calcivis had to reach.

The combination of a phytoprotein and a device presented significant challenges in development. "We had to manage the technical feat of capturing the image of fleeting bioluminescence and also to develop a functional assay for a phytoprotein that is only active for a few milliseconds," said Christie.

In addition, Calcivis had to develop a process for manufacturing the phytoprotein in *E. coli*. "That meant we had to run a novel biologics program alongside a novel medical device technology development program," Christie said.

The origin of Calcivis' technology lies in a eureka moment for the scientific founder of the company, Chris Longbottom, then at Dundee University in Scotland and now assistant director of the Dental Innovation and Translation Center at King's College London Dental Institute.

Bored during a dental convention in the U.S., Longbottom found himself browsing in a Barnes and Noble bookshop, reading about the mechanics of bioluminescence and making the leap between the calcium-fuelled natural phenomenon and the possibility of using bioluminescence as a marker for calcium ions liberated as a result of demineralization of teeth.

The early work in turning the idea into a device was carried out by Christie's then employer, a company applying bioluminescence for monitoring oil and gas pipelines.

Christie is a veteran of the U.K. biotech and devices industry, having previously worked – among other companies – for Powdermed plc, which developed a needle-free injection device, and for PPL Therapeutics plc, the company spun out to commercialize applications of the cloning technology that led to the birth of Dolly, the first cloned sheep. Seeing the potential of Longbottom's device, he formed Calcivis in 2012.

With CE marking in hand and FDA approval hopefully in the offing, Calcivis is poised to begin commercialization. The company currently is looking to raise $10 million in a series E round, to back the U.K. launch and begin to form a U.S. sales and marketing operation.

Since its formation, Calcivis has raised £9.5 million (US$13.5 million), of which £2.5 million was in the form of two non-dilutive grants, from the government innovation agency Innovate UK, and from the EU's Horizon 2020 research program.The lead private equity investor is the Scottish business angel group Archangels, which was joined by U.S. investor Julz Co. LLC, of Chapel Hill, N.C., in the most recent round in September 2017.

The Feb. 13 lift off in the U.K. will be a soft launch to test the market. Calcivis will first target dental practices that have shown an interest during the development of the product. Christie also aims to sell the device to university dental schools, where he hopes the ability to detect demineralization will influence the way in which dentists are trained, and eventually, change the standard of care.

In the U.K., the devices are priced at £1,500 each. There are consumables, in the shape of a disposable tip for applying the phytoprotein to a tooth, at a cost of £9 each, and the protein itself. This comes in the form of a lyophilized powder, ready for mixing with water and loading into the syringe that is built into the handle of the device. ♦

Intended use

Continued from page 1

BioWorld MedTech that the agency's proposed use of a totality-of-evidence standard to impute intent does nothing to clarify what sort of activities would be out of bounds, just one reason that this approach to the intended use controversy is "deeply problematic."

FDA commissioner Scott Gottlieb announced Jan. 12 that the agency would suspend the January 2017 intended use rule in part because the rule also encoded tobacco products, which he hinted lent less clarity rather than more to the commercial speech discussion. The agency reopened the docket for comment through Feb. 5, 2018 (docket no. FDA-2015-N-2002), but industry had already registered its opposition to the use of a totality of evidence to determine whether a drug or device maker intended to illicitly promote its products.

Lee said the intended use provision, "particularly the knowledge requirement, has raised issues of application and interpretation for decades." She said the inclusion of an intended use rule with rulemaking pertaining to tobacco products "was certainly surprising," due to the vast scope of effect of the regulations dealing with the intended use predicament.

"I think the totality-of-evidence standard that has been proposed is deeply problematic," Lee said, because it does not clarify the already nettlesome knowledge requirement, and would do nothing to simplify interpretation of the law generally. The traditional interpretation at the FDA and at the Department of Justice has led to several setbacks in the courts, and Lee said that wherever the federal government lands on these issues, "it needs to reflect recent developments in First Amendment cases." She cited the outcome in *U.S. v. Caronia* and the acquittal of Howard Root in the Vascular Solutions case as among recent examples that demonstrate the difficulties the FDA faces.

"Whether it's an actual revision of the rule or just in how the FDA interprets that, those cases have to animate how FDA applies its expectations" regarding the off-label discussion, Lee said, adding, "I think the fact that the [intended use] proposal was postponed yet again . . . is the best indicator of where the FDA is in its analysis of this issue."

Several states are considering or have already passed laws regarding off-label communication, which would seem to put both FDA and the Department of Justice in a bind, and Lee confirmed that the FDA "is under a lot of pressure to issue guidance or rulemaking, or some sort of statement about where it is landing" on the underlying issues. She confirmed that developments in state legislation may create a federal preemption problem. "The last thing anyone wants to see is a patchwork of [state] laws around what manufacturers can or cannot say," she said, including instances in which a state law is more restrictive than federal law, rather than less.

Still, Lee said there are reasons for optimism. "The delay in the totality-of-evidence discussion" seen in the 2017 intended use rule is "a positive sign. Although I think many have wished for clearer guidance sooner, I think it's more important ultimately that we get to the right answer," rather than expeditiously arriving at a less-than-durable resolution, she said.

Lee said the time seems ripe for FDA to issue clear guidance around these matters, but she noted that the time seemed ripe at several points in the past as well. State law would not affect the federal government's ability to prosecute on commercial speech issues, but defense attorneys would cite state law as a defense, and as is the case with the legalized marijuana predicament, "it will become even more difficult to enforce" federal law, she said.

Smart device makers avoiding warnings

The number of device warning letters was down significantly in fiscal 2017 compared to the prior fiscal year, a development that ran roughly in parallel to the emergence of legislation addressing the device inspection process. However, device makers received a substantially higher number of inspectional forms 483, which would seem to lend little clarity over whether the FDA was easing up on device makers as the politics of inspections played out on Capitol Hill. (See *BioWorld MedTech*, Jan. 4, 2018.)

Lee said the numbers are encouraging despite the confusion generated by the political background noise. "I do think that from the agency's perspective and industry's perspective, [the drop in warning letters] is good news. What it suggests is that companies are able to respond effectively and address the deficiencies," cited in 483s.

The benefit of quicker resolution of 483 citations is that it requires fewer resources for the FDA and the inspected entity, but Lee also noted that device quality has been a hot topic for some time now. "When you take a step back and look at the FDA as a whole, with devices in particular, it's worth mentioning that the FDA over the past five to 10 years has focused on the case for quality" to ensure device makers know what is expected of their quality systems, Lee said.

"Another way of looking at the drop in warning letters is that companies are just addressing these inspectional observations more effectively," Lee said, an indication that the quality campaign by CDRH is having the intended effect.

Warning letter close-out letters do not seem to generate much enthusiasm among device makers, however, but Lee said she is uncertain as to why device makers don't more commonly pursue a close-out letter. Compliance with the latest update to ISO 13485, the international quality management standard, isn't mandatory for another 14 months, but Lee said, "I think companies are on top of that. It's been a long time in coming."

As for the impending do-over of ISO 14971, the risk management framework, Lee said there is little reason to expect a drastic overhaul. "I would characterize it more as a refinement" of 14971, in part because the basic structure of risk management seems to have stood the test of time. She said the citations that typically show up in 483s, such as complaint handling and corrective and preventive action, are two areas where the next iteration of 19471 might provide more detailed guidance. ♦

Multiwave Innovation

Continued from page 1

The company wants to shift the lines of ultra-high field imaging in the clinical field.

"This new technology based on the structuring of materials will help improve the diagnosis of neurological diseases with more detailed analysis of the brain's internal structure," Panos Antonakakis, CEO of Multiwave Innovation, the French subsidiary of Swiss firm Multiwave Technologies AG, told *BioWorld MedTech*.

The resolution of images increases when the magnetic field of the MRI increases: 1 mm resolution at 1.5 tesla, 0.5 mm at 3 tesla, 0.2 mm at 7 tesla. However, as the intensity increases, inhomogeneity of the zones becomes greater and results in a loss of visibility in certain areas. Thus, conventional 7-Tesla birdcage MRIs antennas applied to the head experience a loss of contrast characterized by "the appearance of inhomogeneous areas in three anatomical regions of the brain: the cortex and both temporal lobes," Redha Abededdaïm, research lecturer at the Fresnel Institute of the University of Aix-Marseille told *Bioworld MedTech*. Abdeddaimis one of the co-inventors of this new technology for the ultra-high field MRI antenna.

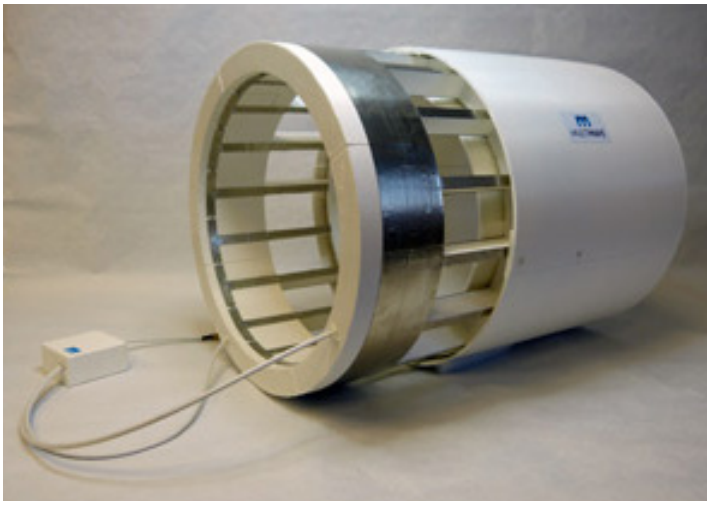
"Our idea was to use metamaterials to optimize the resolution of images by correcting the non-homogeneity of the radio frequency signal and controlling the specific absorption rate," said Tryfon Antonakakis, CEO of Geneva, Switzerland-based Multiwave Technologies AG – and brother of Panos Antonakakis. Tryfon's research focused on the application of homogenization theories for wave propagation in micro structured media in the field of electromagnetism and Multiwave Technologies uses metamaterial technology applications in health care.

"Metamaterials are engineered materials structured above the molecular scale to offer new functionality to any given material," said Tryfon Antonakakis.

Founded in 2016 in Marseille, Multiwave Innovation signed an exclusive license to commercialize the 7T MRI antenna based on a patent of CEA-Neurospin and the Fresnel Institute. The Fresnel Institute and Multiwave Innovation have entered into a co-development agreement to carry out joint R&D on MRI antenna technologies based on the initial patent of 2016. In less than two years, 15 mathematicians, physicists and engineers of Mutiwave Innnovation have developed 10 proprietary software algorithms for optimization, machine learning and homogenization as well as an engineering database. These software developments accelerate the metamaterial design process of the MRI antenna by several orders of magnitude.

A bird cage containing metamaterials

This new generation RF coil, shaped like a bird cage with a 30 cm diameter and weighing less than 5 kg, is comprised of metamaterials in simple shapes (squares, rectangles, ellipses), which have undergone Multiwave Innovation's software algorithm treatment. Non-magnetic circuits passing through the antenna and connected to an electronic board create the resonance field.



Ultra-high field MRI antenna for 7 Tesla MRI scanners; Multiwave Innovation SAS

Three months ago, Multiwave Innovation developed its second transmitting antenna prototype based on metamaterial in accordance with clinical MRI standards. The company is conducting physical performance tests on the antennas in Neurospin's research platforms at the Frédéric Joliot Institute for Life in Saclay. These new antennas allow for weighting and balancing of radio frequency fields while reducing the specific energy absorption rate.

"We are going to start clinical trials on a cohort of 10 patients in 2018," said Panos Antonakakis. The company expects to obtain CE marking and FDA approval in 2019 for the early detection of neurological diseases and other conditions in the brain.

A niche market of more than $281M

Thanks to its technology, Multiwave said it looks forward to competing with other companies that are positioning themselves in the ultra-high field MRI antenna market: Companies from Germany such as Rapid Biomedical Gmbh, MRI Tools Gmbh, MR Coils BV, Nova Medical Inc., Invivo Corp Quality Electrodynamics LLC and Resonance Research Inc. The company said it intends to be one of the prime movers in clinical 7T MRI antennas. Its goal is to sell 10 UHF MRI antennas by 2020 thus capturing 1 percent of the estimated UHF market launched by Siemens Healthineers who has just obtained FDA approval for its Magnetom Terra 7T MRI scanner.

Multiwave Innovation counts more than 20 scientists in its HQ in Marseille and plans to add more as its innovations in the field of MRI antennas continue.

"We're also involved with the M-Cube European program coordinated by Aix-Marseille University in order to develop a UHF MRI antenna suitable for the whole body," said Panos Antonakakis. This project, backed by a European Union four-year study subsidy totaling $4.8 million, includes 10 partners, eight European universities and two SMEs: Multiwave Innovation and the Dutch company MR Coils. ♦

EMA

Continued from page 1

workable," EMA Executive Director Guido Rasi told journalists. "The core business will be run without major disruption."

The agency agreed to this present location having previously rejected another temporary option put forward by the Dutch Ministry of Health, Welfare and Sport and the City of Amsterdam in their winning bid, which was selected on a coin toss last November, following a tie with Milan's offer. (See *BioWorld MedTech*, Nov. 21, 2017.)

Although the EMA will be able to provide accommodation for its 900 staff, it will have to source additional space to handle some of its large volume of meetings. Given its virtual structure – its core staff is complemented by a pool of about 4,500 experts drawn from national drug regulators – it hosts about 36,000 person visits every year.

"It could maybe be better, but it is okay for EMA," conceded Bruno Bruins, the Dutch health care minister during the briefing. "It is a terrific location, with good public transport and a lot of meeting facilities in the neighborhood."

It's just a five-minute train ride from Amsterdam and a 10-minute trip to Schiphol Airport, Amsterdam's highly connected aviation hub.

Using a temporary premises was always part of Amsterdam's plan, as its proposed purpose-built EMA HQ would never have been ready for March 30, 2019, when the U.K. formally exits the European Union. Given the likelihood that the U.K. and the EU will agree to a two-year transition deal up to March 2021 – and given the EMA's long-term lease on its existing building in London – the need for the EMA to up sticks and move to Amsterdam in such a tight time-frame is motivated as much by the political optics around Brexit as by the EMA's mission to evaluate the safety and efficacy of human and animal medicines.

The fact that it will have to move twice, in quick succession, is far from optimal and will inevitably limit the EMA's ability to deliver on projects that are outside its core remit. It has already categorized its various activities in order of their importance. Some projects of lesser importance have already fallen by the wayside and several more will do so during the transition, but any slippage in its turnaround time for marketing authorization applications would quickly draw the ire of the pharmaceutical and med-tech industries and of patients.

An EMA spokeswoman confirmed that its new HQ, the Vivaldi Building, in the newly emerging Zuidan ("South Axis") business district, which is just south of Amsterdam's center and less than 10 minutes from Schiphol airport, will be ready for occupancy in November 2019, two years after the European Council vote.

In the meantime, the EMA has a lot of planning and preparatory work on its hands. As well as ascertaining the intentions of its permanent staff – Rasi said the agency is waiting on detailed information on international schools before it polls its staff on their plans – the EMA is also trying to define the shape of its future relationship with the U.K.'s Medicines and Healthcare products Regulatory Agency (MHRA).

> *"It's a less comfortable solution, but it's workable.*
>
> Guido Rasi
> EMA executive director

"We are working hard with the U.K. authority to try to figure out all the technical work that has to be done," Rasi said. Whether the MHRA will remain part of the EMA system after Brexit is essentially a political decision that is out of the hands of both agencies, but given MHRA's prominent role in the EMA network, disentangling the two would add further complexity to the EMA's transition to the Netherlands.

At a political level, uncertainties about the direction of the Brexit project abound at present. European Commission officials and senior European leaders – notably Germany's chancellor Angela Merkel – are becoming increasingly public in their irritation at the U.K. government's lack of a clear policy on Brexit, while the divide in the ruling Conservative party between those who favor a clean break with the EU – a "hard Brexit" – and those who wish to maintain deep trading and regulatory links with the bloc – is becoming increasingly fractious.

The U.K.'s prime minister, Theresa May, whose minority administration is propped up by the Democratic Unionist Party of Northern Ireland, is coming under increasing pressure from the Brexit hardliners within her party. Her political authority is already weak, and some commentators predict that a poor showing in local council elections on May 3 could finish her off completely. In that context, it is difficult to predict with any degree of confidence the likely future role of the MHRA in the European system of drug regulation. ♦

Other news to note

San Diego-based **Illumina Inc.** reported a federal jury in San Francisco ruled in its favor in a patent infringement suit against San Jose, Calif-based **Ariosa Diagnostics Inc.**, now owned by **Roche**, determining that the latter's prior and current Harmony noninvasive prenatal test infringed on U.S. patents 8,318,430 and 7,955,794. Illumina was awarded about $26.7 million for past damages by a jury. Counterclaims by Ariosa that Illumina breached a supply agreement by bringing the lawsuit were rejected by the jury. Illumina plans to seek injunctive relief for ongoing infringement by Ariosa's continuing sale of its Harmony test. The U.S. patent and trademark office previously upheld the validity of the patents in multiple challenges filed by Ariosa.

Malaria

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falciparum, infecting more than 200 million people worldwide and killing around 650,000 each year.

Despite considerable success in reducing the prevalence of malaria, its incidence, including in visitors to endemic areas, has continued to increase steadily.

"There is currently no completely effective vaccine for malaria and no single totally reliable approach to prophylaxis," said co-lead researcher Andrew Owen, a professor in the University of Liverpool's Department of Molecular and Clinical Pharmacology.

"Daily oral administration of antimalarial drugs is currently used for prophylaxis but must be combined with other strategies such as insect repellent, appropriate clothing and using insecticide-treated bed nets," Owen told *BioWorld MedTech*.

The best currently available means of pharmacological malaria prophylaxis are antimalarial tablets. However, healthy people must be strictly compliant with those to achieve effective prophylaxis.

"Although antimalaria drugs exist, they require individuals to take the medication daily," said study co-lead researcher Steve Rannard, a professor in the University of Liverpool's Department of Chemistry.

However, "chronic oral dosing has significant complications arising from the high pill burden of many patients across populations with varying conditions leading to non-adherence with preventative therapies," Rannard told *BioWorld MedTech*.

The objective of the new study was to use nanotechnology to improve existing antimalarial drug delivery in a novel injectable form, which could maintain blood drug concentrations long after a single dose.

Nanotechnology involves manipulating matter on an atomic, molecular and supramolecular scale, for use in the diagnosis, prevention or treatment of disease.

Solid drug nanoparticles (SDNs) are one such nanotechnology that can help enhance drug exposure and improve treatment or prevention of diseases, including HIV and malaria.

The Liverpool team had previously shown SDNs to be effective for oral drug delivery, but this is the first time they have shown benefits for a long-acting injectable (LAI) format. Injected intramuscularly, SDNs establish a drug depot, releasing medicine into the bloodstream over an extended period.

Using that technology, the trans-Atlantic research team developed an LAI version of the daily antimalarial oral atovaquone (Mepron, Glaxosmithkline plc).

Mice injected intramuscularly with the nanomedicine achieved prophylactic blood concentrations and were completely protected from malaria for 28 days, the researchers reported in the Jan. 22, 2018, online edition of *Nature Communications*.

"Mice were injected with the SDN atovaquone formulation, and after 28 days mice were intravenously exposed to *P. berghei* sporozoites. They were then monitored for 42 days for parasites, and if none were seen, deemed to be protected, while none of the control mice were protected," said Owen.

"*P. berghei* strain Anka is an accepted preclinical model for malaria because mice cannot be infected with *P. falciparum*, which is restricted to great apes and humans," he explained. "Current oral medicines containing atovaquone are active against *P. falciparum* and *P. vivax* malaria, although possibly only primary infection by the latter. However, since our nanotechnology does not alter the drug's chemistry, one would expect efficacy against these strains to depend upon achievable blood concentrations after administration," said Owen.

> *"Our research seeks to remove the need for daily tablets and generate long-acting dosing technologies that may be able to provide therapeutic drug concentrations for months after a single administration.*
>
> Steve Rannard
> University of Liverpool

"This is the first demonstration of LAI delivery using SDNs created using our proprietary approach of emulsion-templated freeze-drying" (ETFD), he said.

Owen pointed out that while LAI formulations have been developed for indications such as contraception, schizophrenia and HIV, "we believe ETFD has a number of explicit benefits, including compatibility with preferred agents, scalability and cost."

Since mice eliminate atovaquone more rapidly than do humans, a longer duration of protection might be expected in people. "Although our formulations achieved 28 days protection in mice, the half-life in humans is eight times slower than in mice, so the protection will almost certainly be longer than 28 days," said Owen.

"Our research seeks to remove the need for daily tablets and generate long-acting dosing technologies that may be able to provide therapeutic drug concentrations for months after a single administration," said Rannard.

"This would provide a clinically relevant intervention that could readily impact large numbers of people and significantly prevent transmission of malaria," he added.

"This ability to protect from malaria infection may provide an additional tool in the arsenal used to combat malaria in non-immune travelers and residents of endemic areas," noted Owen.

"Since atovaquone is already licensed for use in humans and the nanomedicine contains excipients to stabilize the formulations that are already used in other medicines, it could enter clinical trials within a very short timescale," he predicted. "As an academic group, our main barrier is funding to take the formulation forward, but our trans-Atlantic collaboration has the expertise to scale the formulations and conduct clinical trials, which with sufficient resources could begin within 18 to 34 months."

Owen noted that while studies have shown that atovaquone alone is an effective prophylaxis against malaria, drug combinations are required in patients already infected with the parasite, most commonly atovaquone plus proguanil.

However, "proguanil doesn't lend itself well to this nanotechnology so we may need to be creative," he said. "If other drugs can be manufactured in this way, there is also potential for a long-acting combination therapy for malaria." ♦

Product briefs

Accuray Inc., of Sunnyvale, Calif., reported that data from a study of 138 patients with trigeminal neuralgia showed stereotactic radiosurgery (SRS) delivered with the Cyberknife system resulted in rapid and long-lasting pain relief, with minimal side effects. The study, titled "Image-guided robotic radiosurgery for trigeminal neuralgia," was published in the December 2017 issue of the peer-reviewed journal *Neurosurgery* and provides robust clinical data supporting the efficacy and safety of the system for TN patients.

Bellerophon Therapeutics Inc., of Warren, N.J., said enrollment in its phase III Inovation-1 study evaluating Inopulse in patients with pulmonary arterial hypertension now exceeds 100 patients, representing more than half of the anticipated enrollment. As previously agreed with the U.S. FDA, an interim analysis of this trial will be performed by the data monitoring committee when half of the subjects complete the 16-week blinded treatment phase. The interim analysis will determine if the study should be stopped early for efficacy or futility, continued as planned, or if the trial size should be increased. Bellerophon anticipates the readout of the interim analysis in mid-2018, and the availability of top-line data from the full study toward the end of 2018. The Inopulse delivery system delivers pulsatile inhaled nitric oxide, allowing for use in a portable chronic setting.

Valencia, Calif.-based **Bioness Inc.** received a medical device license from Health Canada for its Stimrouter neuromodulation system for the treatment of chronic peripheral nerve pain (excluding the cranial facial region). The Canadian medical device license provides approval to commercialize Stimrouter and begin sales throughout Canada.

Medtronic plc, of Dublin, reported the initiation of its investigational device exemption (IDE) study for the Abre venous self-expanding stent system. The Abre IDE study will evaluate the safety and effectiveness of the Abre stent in subjects with iliofemoral venous outflow obstruction. The first procedure was performed in December of 2017 at Sanger Heart & Vascular Institute in Charlotte, N.C. The multicenter, single arm study intends to enroll 200 subjects with deep venous disease from up to 35 sites throughout the U.S. and Europe. The primary efficacy endpoint will evaluate patency at 12 months, which is defined by freedom from occlusion and freedom from clinically driven target lesion revascularization. The primary safety endpoint will evaluate the incidence of composite major adverse events at 30 days following stenting of an obstruction in the iliofemoral venous segment. Data from the study will be used to support the Abre stent U.S. premarket approval application for the treatment of symptomatic iliofemoral venous outflow obstruction in patients with venous occlusive disease.

Medymatch Technology Ltd., of Tel Aviv, Israel, was granted expedited access pathway designation by the U.S. FDA for intracranial hemorrhage detection (ICH). This software medical device, based on deep learning technologies, automatically analyzes non-contrast head CT images. It is designed to alert the treating physician when ICH is detected.

Financings

Nottingham, U.K.-based **Oncimmune Holdings plc**, an early cancer detection company and developer of Earlycdt liquid biopsy platform technology, entered into a license agreement and completed £7 million (US$9.85 million) equity subscription with Genostics Company Ltd. This is the first tranche of a total £10 million (US$14.07 million) equity investment in Oncimmune, which was agreed as part of a license, distribution, manufacturing and future development agreement for all products related to the platform for patients in China. Genostics will invest £10 million (US$14.07 million) in Oncimmune by way of subscription for 6,410,256 new ordinary shares at a price of £1.56 (US$2.20) per ordinary share, a 49 percent premium to the share price of 105p (US$1.48) at market close on Dec. 29, 2017. The second tranche of £3 million (US$4.22 million) will be paid by March 30. An application has been made for the 4,487,179 ordinary shares under this first subscription to be admitted to trading on admission, expected Feb. 2. Under the terms of the license, Oncimmune will receive a royalty of 8 percent to 12.5 percent on the gross revenue subject to aggregate minimum royalty payments over the first six years post market entry of £15.7 million (US$22.10 million) and £5 million (US$7.04 million) per year thereafter. Genostics will sell Earlycdt-Lung within 36 months of the date of the agreement, subject to CFDA approval. Genetech, of Shanghai, a subsidiary of GGH, will be responsible for the manufacturing, marketing and distribution of the platform. The agreement may also lead the two firms to discuss a possible move to production in China and investment in R&D for additional cancer detection tests. A representative from Genostics will be appointed to Oncimmune's board.

Cardiology Extra

Keeping you up to date on recent developments in cardiology

By Katie Pfaff, Staff Writer

Spontaneous subarachnoid hemorrhage stroke increasing in pregnant women

A rare stroke occurrence, spontaneous subarachnoid hemorrhage (sSAH) in which arteries in the brain become weak and rupture leading to bleeding in the membranes around the brain, is on the rise among pregnant women, according to the American Heart association/American Stroke Association meeting in Los Angeles Jan. 24. Research was presented at the meeting from a review of Health care Cost and Utilization Project's Nationwide Inpatient Sample records of 3,978 pregnant women ages 15 to 49 between 2002 and 2014. According to the data, pregnant women admitted to the hospital jumped from 4 to 6 percent; sSAH was highest among African American women at 8 percent, Latina women at 7 percent and white women at 4 percent; and percentage of sSAH was highest among patients between 20 and 29 years old (20 percent) while lowest among patients aged 40 to 49 (1 percent). However, pregnant patients with sSAH improved after admission compared to non-pregnant women with the condition. Pregnant women were more likely to be discharged home after sSAH versus non-pregnant women with sSAH, and pregnant women with sSAH died eight percent of the time compared to 17 percent of women who were not pregnant and suffered sSAH. "We need to increase awareness in the medical community about the increasing trend of spontaneous subarachnoid hemorrhage in pregnancy because management of these patients continues to be a clinical conundrum," said study lead author Kaustubh Limaye, clinical assistant professor, division of cerebrovascular diseases, University of Iowa in Iowa City. "Pregnant women with spontaneous subarachnoid hemorrhage may have better outcomes than previously expected, which challenges prior findings from small, single-center reviews." Limaye's salary was partly supported by the National Institute of Neurological Disorders and Stroke.

Study looks to guidelines as bellwether in hospital quality in heart failure

According to a *Circulation* journal study, "Association between hospital volume, processes of care, and outcomes in patients admitted with heart failure: insights from get with the guidelines-heart failure," published Jan. 29, 2018, quality of a hospital's care may be evaluated better by looking at adherence to guidelines rather than the number of heart failure (HF) patients admitted. The study of 125,595 patients age 65 and older with heart failure treated at 342 hospitals participating in the American Heart Association's "Get with the guidelines" heart failure program from 2005 to 2014 indicated those hospitals with greater volume (which ranged from five to 457 HF patients) adhered better to process such as testing, therapy, and smoking cessation counseling. Large volume HF hospitals also were more likely to prescribe cardiac resynchronization therapy devices and implantable cardioverter defibrillators. Differences in mortality while in the hospital, readmission, or death after 30 days correlated with guideline adherence across large and small-volume HF hospitals, though readmission and mortality at six months decreased with followed guidelines. "There is a feeling that hospitals that perform more procedures or treat more patients for a certain condition are likely to have better outcomes," said lead study author Dharam Kumbhani, assistant professor of medicine and a cardiologist at UT Southwestern Medical Center in Dallas. "But what we have found in this study, and others we have conducted, is that patients at hospitals with established processes of care fare better. Going to a high-volume medical center for heart failure doesn't guarantee that you'll have the best outcomes," Kumbhani said. "Identifying the hospitals that provide the best care is more complicated than that, and patients and health policy makers should recognize that smaller-volume hospitals can deliver outstanding care." Many of low-volume HF hospitals are located in rural areas, where patients may not have limited access. Study limitations include that AHA's guidelines program was voluntary and therefore may have impacted results.

Majority of stroke survivors don't meet AHA guidelines

Less than one in 100 patients who survived a stroke meet the seven goals for cardiovascular health laid out by the American Heart Association, according to a poster presentation Jan. 24 at the American Stroke Association's international conference in Los Angeles. The "Life's Simple 7" goals include regular exercise, healthy diet, maintaining normal BMI, not smoking, managing normal blood pressure, blood sugar and total cholesterol. Based on representative sample of 67,514 adults across the U.S. between 1988 and 2014, 1,597 had prior stroke and had data for all measures. Fewer than one in five stroke survivors met four ideal health metrics during the study period. Those who met none or one of the goals was 18 percent between 1988 and 1994, but jumped to 35 percent in 2011 to 2014. Other data changed between the two time periods, including: high blood pressure decreased (45 percent in first time period, 26 percent in second); high cholesterol dropped (37 percent to 10 percent for differing time periods); obesity increased (27 percent to 39 percent); prediabetes/diabetes jumped (49 percent to 56 percent); and those with poor diet increased (14 percent to 51 percent). The study was funded by Roxanna Todd Hodges Foundation.