BioWorld MedTech

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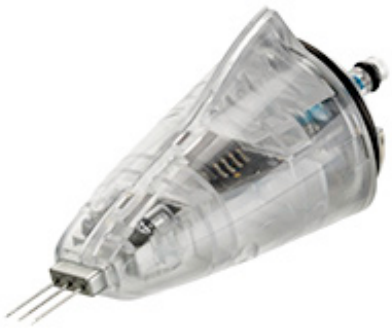

Iovera Smart Tip 309; Myoscience Inc.

Myoscience providing opioid alternatives with launch of Iovera Smart Tip system

By Liz Hollis, Staff Writer

Aiming to help a broader patient population and provide an alternative to opioids, Myoscience Inc., of Fremont, Calif., reported the commercial launch of the Iovera Smart Tip 309.

The launch adds to the company's Iovera system, which treats the genicular nerves through a process called cryoneurolysis. Specifically, it helps patients recovering from total knee arthroplasty surgery, as well as those suffering from chronic knee pain.

Of note, the Smart Tip 309 is intended to help a broader patient population, including those with a

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Inside

FDA gives breakthrough designation to first potential IVD test for Alzheimer's to Fujirebio

By Stacy Lawrence, Staff Writer

Diagnostics for Alzheimer's disease (AD) are improving as biomarker and imaging data continue to improve. Fujirebio Diagnostics Inc. is seeking to offer a further advancement on this front – and the U.S. FDA has reached out with a gesture of support by extending a breakthrough device designation to its Lumipulse G β-Amyloid Ratio (1-42/1-40) quantitative in vitro diagnostic test.

If approved, this could be the first in vitro

See Fujirebio, page 4

BGN's AI platform for ALS progression holds key to improving care and treatment

By David Ho, Staff Writer

HONG KONG – Israel's BGN Technologies Ltd. has developed an AI-driven precision medicine platform for monitoring and predicting the progression of neurodegenerative diseases.

The platform from the technology transfer company of Ben-Gurion University (BGU) is currently focused on amyotrophic lateral sclerosis (ALS; also known as Lou Gehrig's disease).

The company believes the technology holds the potential for improving both personalized patient care and drug development.

See BGN, page 5

Stakeholders revolt over Medicare hit to ultrasound rates

By Mark McCarty, Regulatory Editor

The U.S. Centers for Medicare & Medicaid Services (CMS) has been advised to trim spending on imaging, and the agency has proposed to reset the practice expense component for ultrasound imaging procedures in the draft physician fee schedule for 2019. While CMS eased back from implementing cuts for the current year, stakeholders are scrambling to make the case that the policy is ill-advised and may restrict access, a scenario that could ultimately take a bite out of sales of ultrasound equipment.

The Medicare Payment Advisory Commission had

See Medicare, page 6

Researchers plan phase III GDNF trial in Parkinson's; delivery device is key

By Nuala Moran, Staff Writer

LONDON – Researchers in the U.K. are moving ahead with plans for a phase III study of glial-derived neurotrophic factor (GDNF) in Parkinson's disease, after overcoming the obstacles to repeated delivery of the drug directly into the brain that confounded previous studies.

See GDNF, page 7

BioWorld MedTech's Orthopedics Extra

Executive Editor Holland Johnson on one of med-tech's key sectors

Read this week's edition

Financings

Genfit, a late-stage biopharmaceutical company in Loos, France, dedicated to the discovery and development of therapeutic and diagnostic solutions in metabolic and liver related diseases, filed a registration statement on form F-1 with the U.S. Securities and Exchange Commission relating to a proposed IPO of its American Depositary Shares (ADS), each representing one ordinary share, in the U.S., and a concurrent private placement of its ordinary shares in Europe and other countries outside the U.S. and Canada. The number of securities to be sold and the price range for the proposed global offering have not yet been determined. The company applied to list its ADSs on the Nasdaq Global Market under the ticker symbol "GNFT." The ordinary shares are listed on Euronext Paris under the symbol "GNFT."

Richardson, Texas-based **Ikonopedia Inc.**, which focuses on breast reporting and tracking, said that Texas Women Ventures (TWV) Capital, an independent Dallas-based private equity firm that focuses on women-owned and women-led businesses, has invested in the company. The TWV investment was part of Ikonopedia's $2 million series C preferred stock financing. Proceeds will fund key product development initiatives and fuel continued growth of the company's customer base and exam volume. Whitney Martin, managing director and co-founder of TWV Capital, will join the Ikonopedia board.

Masimo Corp., of Irvine, Calif., has filed a prospectus of a mixed shelf registration. The company noted that an unspecified number of the identified class of securities is being registered for possible issuance from time to time at indeterminate prices. The company said it intends to use the net proceeds from the sale for general corporate purposes, including acquisitions of companies and technologies, capital expenditures, working capital and repayment or refinancing of any debts it has outstanding or may incur.

Eagan, Minn.-based **Precision Therapeutics Inc.** reported the pricing of its public offering of its common stock and warrants to purchase common stock, with anticipated gross proceeds of up to $1.26 million, before deducting placement agent fees and expenses and offering expenses. The company is offering 1.4 million units on a "best efforts" basis, with each unit consisting of one share of common stock and a warrant to purchase 0.5 of a share of common stock, at a price of $0.90 per unit. The warrants are immediately exercisable at a price of $1 per share of common stock and will expire on the fifth anniversary of the date of issuance. The offering is expected to close on or about March 1.

Santa Clara, Calif.-based **Shockwave Medical Inc.** set the terms of its IPO, saying it is offering 5 million shares of its common stock. It estimated that its IPO price per share will be between $14 and $16. The company has applied to list its common stock on the Nasdaq Global Market under the symbol "SWAV." The company estimates that the net proceeds will be about $66.6 million, or roughly $77 million if the underwriters exercise their over-allotment option in full, assuming an IPO price of $15 per share. Net proceeds of this offering, together with existing cash and cash equivalents, will go toward sales and marketing activities to support the ongoing commercialization of its intravascular lithotripsy system, R&D and clinical studies and working capital and general corporate purposes.

Tel-Aviv, Israel-based **Zsquare**, which has developed the Multiply single-use endoscopic platform, secured $10 million in financing for the development of its Multiply Mini 0.45 mm fiber endoscope, with an eye toward expedited FDA 510(k) clearance. The round was led by Chartered Group.

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Myoscience

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high body mass index (BMI). "Iovera is a simple, needle-based procedure that uses proven cryotherapy to relieve pain," Tim Still, president and CEO of Myoscience, told *BioWorld MedTech*. "It's very immediate, very safe," and gives long-lasting relief. He also noted that the technology has gained commercial traction in the last 24 to 36 months.

Freezing the nerves

The system's smart tips deliver precise, controlled doses of cold to freeze peripheral nerves, producing an immediate and long-lasting nerve block.

Clinicians have expressed enthusiasm about the system. "Many patients are looking for non-opioid solutions for managing pain. I have found the Iovera therapy to be an important option to provide lasting pain relief to my patients, resulting in at least a 50 percent reduction in opioid use over the entire recovery period after a total knee replacement. This therapy is a remarkable step forward for patients undergoing total knee replacement, which can cause acute and chronic pain in the months following surgery," said Pieter Vreede, anesthesiologist at Riverview Health in Noblesville, Ind. He noted that the Smart Tip 309 will provide the opportunity for ease of access to deeper nerves in patients with a high BMI.

Standing alone

"We don't really have direct competition," Still added. "The primary purpose is to reduce the use of opioids and [the] pain that's associated with surgery, recovery and chronic conditions." Specifically, the platform is in use in the orthopedic market for those undergoing total knee replacement and osteoarthritis.

"It absolutely can," Still answered when asked whether the technology can be used in areas beyond the knee. "One of the challenges that the company had frankly in the early days was looking at all of the applications of the platform and where to focus." He added that there is a potential for the platform in shoulders, the lower back, ankle and hips.

Moving forward

"Plans for us basically will be to continue to take advantage of the commercial progress that we've had," Still said of where he saw the company going in the next 12 to 18 months. "We've been doubling sales year-over-year, [and] there is quite a bit of market opportunity just in the total knee space."

He noted that the company finished last year with about $5.5 million in sales, but there is room for growth. In addition, there is a lot of interest in expanding to the additional indications in other joints. The company hopes to do some clinical work in those areas in the near term, but it plans to continue to place a special emphasis on total knee. "If you look at the end of 2018, some of our market data estimates that there are about 950,000 total knees done on an annual basis," he said, noting the company has penetrated less than 2 percent of the total market.

When asked about geographic focus, he said the company is concentrating on the U.S., but it is in the process of gaining the CE mark. The company will feature the Smart Tip 309 at the 2019 American Academy of Orthopaedic Surgeons Annual Meeting between March 12 and 16 in Las Vegas.

Last fall, the company reported that it had completed enrollment in its randomized, controlled trial at the Campbell Clinic in Memphis, Tenn. It enrolled 125 patients to evaluate the effect of cryoanalgesia using the Iovera system to the standard of care for managing pain after total knee replacement surgery. The goal was to demonstrate how cryoanalgesia can significantly reduce opioid consumption after the procedure, and lead to improved physical function and enhanced recovery. ♦

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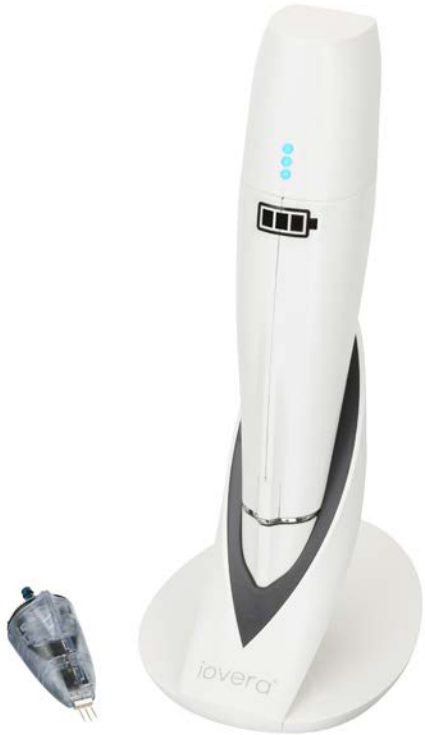

Iovera system with Ukiah; Myoscience Inc.

iovera° | myoscience

Fujirebio

Continued from page 1

diagnostic (IVD) test to assess patients who may have AD. But it is still expected to be used in conjunction with other diagnostic tools such as neurological examination, neurobehavioral tests, imaging and routine laboratory tests.

Still, the Lumipulse beta amyloid test could conceivably obviate the need for a costly PET scan, which is often currently seen as the definitive test for AD. Fujirebio claims that a negative Lumipulse is consistent with a negative amyloid PET scan – and vice versa, that a positive Lumipulse result is consistent with a positive PET scan result. PET imaging, however, isn't routinely covered by payers for AD diagnostics.

"We are working diligently to make this important test available to patients in the near future. Accurate diagnosis is essential for appropriate medical care as the number of Alzheimer's disease patients is expected to increase to 14 million Americans by 2050," Hiroshi Sekiya, senior product manager at Fujirebio U.S., told *BioWorld MedTech*. "We also believe a commercially available CSF IVD test will enable increased ability to determine amyloid presence in clinical trials and research projects, and in addition lead to reimbursement activities. We will continue to announce milestone achievements as we progress through the process."

The company declined to offer clinical study plan details or a timeline for FDA submission; it did say that throughout this year it would gather clinical data from multiple sources to support a submission.

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> Senior product manager, Fujirebio U.S.

Lumipulse G β-Amyloid Ratio (1-42/1-40) is a quantitative test using human cerebrospinal fluid to estimate the presence of amyloid pathology in adult patients age 50 and older. Assessing levels of beta amyloid has been established in both clinical and research use as helpful in evaluating AD and other causes of cognitive decline.

An IVD test, rather than the more common and less regulated laboratory developed tests that receive CLIA (Clinical Laboratory Improvement Amendments) certification, could make it easier for a wider range of health care providers to offer standardized diagnostics. That, in turn, is expected to potentially lower costs to providers.

A long history of failure

In May 2018, Fujirebio partnered with Janssen Pharmaceuticals

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BGN

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According to BGN Technologies, the platform works by analyzing demographic and clinical data using machine learning and data mining algorithms to produce models that can predict the rate and pattern of ALS progression.

Boaz Lerner, an associate professor of the Department of Industrial Engineering and Management at BGU who developed the platform, told *BioWorld MedTech* that the platform's machine learning algorithms uses retrospective clinical data of patients (such as demographics, vital signs, and lab test results) to reliably stratify the heterogeneous ALS population into smaller homogenous sub-groups.

Improving clinical trial design

The platform would improve the design of clinical trials, by providing more accurate predictions of disease progression.

It also provides identification of interrelationships between demographics and measurable factors from physical examinations and patient functionality that will advance clinical research.

According to BGN Technologies, the research and drug development of this condition is complicated by the heterogeneity of the ALS population leading to variability in symptoms at onset, disease progression rate and pattern and survival.

"In addition to improving clinical trials, another benefit of the platform is the ability to reduce uncertainty and improve the patient's and caregiver's quality of life," said Lerner.

"The novelty of our system stems from its ability to stratify the heterogeneous ALS population to homogenous sub-groups and, in addition, to predict the expected change in specific patient's functionalities, such as walking, speech and writing," said Lerner.

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> Associate professor, BGU

Predicting ALS progression

It enables researchers and caregivers to predict progression rate and pattern of ALS for new patients, based on their clinical representations in the data.

"If we can predict, for example, that the patient's walking or speech ability will deteriorate in six months, he or she can organize the home to address their needs or move to a more appropriate environment, or start looking for a specific device to communicate with people," said Lerner.

He added that this will also enable physicians to know where to begin specific treatment, whether and when to focus on the respiratory system or physiotherapy.

The platform was developed using data from clinical trials and tested on similar data of other patients that were new to the platform. The algorithms and the disease progression prediction will improve as more clinical data is added for each patient.

"One of the big challenges of designing and managing clinical trials for ALS stems from the fact that not only is it a rare disease, but also clinical heterogeneity makes it hard to identify markers correlating with disease severity for enabling successful clinical trials," explained Lerner.

"As a result, after decades of research, there is still no real cure for ALS and other neurodegenerative diseases, such as Alzheimer's disease."

What's next?

Lerner said the next stages will include installations in medical centers for testing and further validating the system on clinic data.

"The funding we recently received from the Israel Innovation Authority will enable researchers to create a system that can be implemented on PCs, the cloud, and cellular applications for personalized monitoring and prediction of ALS progression for the sake of patients, physicians, caregivers, pharmaceutical companies and health maintenance organizations," said Itzik Mashiach, business development personnel at BGN Technologies.

BGN Technologies is also now on the lookout for an industry partner for the further development and commercialization of the platform.

"We are looking for two kinds of partnerships. One, is an industry partner to license the technology or for the further development and commercialization of the platform for improving clinical trial," said Lerner. "And in parallel, we are also seeking investment for the possibility of establishing a startup company based on this promising technology."

The company believes the platform has further potential to be adapted for other neurodegenerative diseases later on.

"The platform is broadly applicable for neurodegenerative diseases. The plan is to test the algorithms on the data of patients with Alzheimer's and Parkinson's diseases and then adjust the algorithms accordingly, similar to the procedure we used for ALS," said Lerner. ♦

Medicare

Continued from page 1

recommended in June 2018 that CMS should consider trimming rates for a number of specialties, including radiology, in order to provide more resources for evaluation and management (E&M) services. MedPAC said E&M services had become undervalued over time, adding that a budget-neutral method for improving rates for E&M would be to cut rates for other services, including imaging. The commission also noted that efficiency gains in these other services are more easily obtained than is the case for E&M, which ordinarily consists almost entirely of a clinician's time.

The American College of Radiology (ACR) and the Ultrasound Access Coalition (UAC) said in a September 2018 statement that their representatives had met with CMS officials to discuss the proposal to revise the direct practice expense input for the calendar year 2019 Medicare physician fee schedule (MPFS). The draft MPFS, the two groups said, would have cut overall payment rates for ultrasound services by roughly nine percent in the current calendar year thanks to the agency's presumed costs for equipment and supplies used in ultrasound and vascular ultrasound.

The ACR and the UAC said the methodology employed by government contractor Strategygen Consulting of Columbia, Md., was not particularly transparent, and questioned the validity of the data sources and the methodology employed by Strategygen, not the first time the company's methods have come under fire. Several of the comments filed for the draft MPFS reflected misgivings about Strategygen's methods, although much of that criticism was leveled by industry. Both the Medical Device Manufacturers Association and the Advanced Medical Technology Association expressed skepticism about the contractor's approach to determining direct practice expense inputs, including in the context of equipment used in stereotactic radiosurgery procedures. (See *BioWorld MedTech*, Sept. 11, 2018.)

Contractor pick a surprise

Tim Trysla, an attorney with Alston & Bird's D.C. office, told *BioWorld MedTech* that it appeared that Strategygen had relied almost entirely on hospital ultrasound cost data rather than incorporating data from free-standing imaging clinic data as well. "Having been at the agency, I was a little surprised at the type of contractor the CMS selected" for the imaging cost data, Trysla said, stating that the company's prior government contracting experience was with the U.S. Department of Housing and Urban Development.

Trysla, who was speaking on behalf of the UAC, said he would have expected CMS to hire a contractor with an established track record in this kind of data collection effort. To expect a contractor "to jump into the [physician] fee schedule cold and understand this process was suspect," he said, but Trysla also noted that neither ACR members nor device makers who were contacted by the two groups indicated they had heard from Strategygen regarding their cost data.

CMS is said to have set aside $2 million for the survey undertaken by Strategygen, but Trysla said that amount might have been insufficient to finance a legitimately exhaustive cost survey project.

Whether CMS will treat the data collected by ACR and UAC as more representative of non-hospital spending on ultrasound equipment is unknown, but Kathryn Keysor, senior director of economics and health policy at ACR, said the groups were following the same process as used by the relative value update committee administered by the American Medical Association. "There's a very stringent requirement for paid invoices" to demonstrate the actual cost of setting up and equipping an ultrasound lab, including for vascular ultrasound labs, Keysor said of the ACR/UAC survey effort. Trysla said that CMS might not be statutorily empowered to use the associations' data to rethink the proposition, but that the groups believed it was nonetheless critical to provide the agency with cost data from non-hospital providers in an effort to set the record straight.

GSA data said to have been included

Trysla said there is some evidence that the Strategygen report did not include an exhaustive set of invoices from across the various clinical settings, but might have relied to some extent on prices as listed by the General Services Administration (GSA). He said Strategygen advised the agency not to use GSA data, but that CMS "didn't take their own contractor's advice, and accepted the GSA data." The point for ACR and AUC is not so much whether there is a well-supported cost point for ultrasound labs and equipment, but that the numbers provided by Strategygen are almost certainly off the mark by a substantial margin.

The proposed reduction of roughly nine percent in 2019 would have been the first in a four-year transition during which the reset of relative values for several CPT codes would have cut rates by as much as 42 percent. The technical component for CPT code 93970 – an ultrasound study of the extremities invoked in anticipation of several treatments, including treatment of deep-vein thrombosis – would have taken a relative value hit of 36.8 percent over four years, a move not likely welcome by cardiologists concerned about peripheral artery disease and its effects on circulatory system health.

Trysla said that hospitals and hospital groups can obtain price breaks for purchases of multiple pieces of equipment, an advantage not usually enjoyed by free-standing imaging clinics. He said the site-of-service argument might have a home in this particular debate, but added, "right now, we're just trying to make sure the physician office practice expense is accurate."

The two groups have advised at least some of the inhabitants of Capitol Hill regarding the dilemma, but Trysla said, "right now, we are focused on educating the industry and providers to get an adequate number of invoices so we can have adequate information" to present to CMS. "We think the process will work if the information is correct, and that's what we're banking on," Trysla said. ♦

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>
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> Alston & Bird

GDNF

Continued from page 1

The automated delivery device, developed by neurosurgeon Steven Gill, was successfully implanted in 41 patients who took part in the phase II trial. They received a combined total of 347 of 350 scheduled monthly infusions over the 40-week blinded stage of the trial, with no serious safety concerns.

The convection enhanced delivery device administered GDNF in a controlled way, with PET scans showing the drug diffused throughout the putamen.

"This trial has shown we can safely and repeatedly infuse drugs directly into a patient's brain over months or years, through a small implanted port that emerges through the skin behind the ear," Gill said. "This is a significant breakthrough in our ability to treat neurological conditions such as Parkinson's."

It is unfortunate then, that the phase II trial, results of which are published in two journal papers Wednesday, just failed to reach the primary endpoint, of a statistically significant improvement in the unified Parkinson's disease rating score (UPDRS), compared to placebo.

Patients receiving GDNF in the first nine months of the trial saw a 17 percent improvement in symptoms, compared to 12 percent in the placebo arm. There was a large variance in response, with some patients improving much more than others. Nine of the GDNF group improved by more than 35 percent in the double-blind part of the trial.

In the second part of the trial, in which all patients received GDNF, there were again improvements in both groups of patients, with no statistical significance between the two.

However, there was a significant difference between the group which received GDNF for the full 18 months of the trial and the patients in the blinded placebo group at nine months.

"Between nine and 18 months, the GDNF group continued to get better; by the end they were 30 percent better, but all had improved," said Gill, professor of neurosurgery at Bristol University.

Gill told *BioWorld MedTech* a number of factors played into the failure to reach the primary endpoint. Those included the need for caution in dosing, evidence that neurotransmitter release was initiated by administration of the infusate in the placebo arm and the fact that UPDRS gives a low weighting to reductions in the amount of "off" time patients experience when levodopa starts to lose its effect.

All 41 patients had been experiencing motor symptoms for five years at the start of the trial. Thirty-seven of them showed clinically meaningful improvements in their symptoms at the end of the study.

After nine months, there was no change in the PET scans of those who received placebo, whereas scans showed regrowth of dopaminergic neurons in all treated patients.

Alan Whone, principal investigator, said the improvement in brain scans is beyond anything seen previously in trials of surgically delivered growth factor treatments for Parkinson's disease.

The failure to produce the same effect on symptoms could be for a number of reasons. "It may be that the effects on symptoms lag behind the improvement in the brain scans, so a longer double-blind trial may have produced a clearer effect. It's also possible that a higher dose of GDNF would have been more effective, or that participants at an earlier stage of the condition would have responded better," said Whone.

Despite not reaching the endpoint, Gill said, taken as a whole, the EMA and FDA agree the data indicate GDNF is "neurorestorative." The regulators have given approval to the phase III trial design, which will use four times the dose of the phase II.

The delivery challenge

Gill has been pursuing delivery of GDNF for the past two decades. He conducted the first open-label trial, in which the growth factor was administered to five patients daily for 18 months, through an indwelling catheter.

All five showed improvements, with "off" periods of severe immobility that occupied 20 percent of their waking day before surgery completely eliminated after six months.

GDNF owner Amgen Inc. picked up the baton, but in late 2004 halted a 48-patient phase II study, citing limited efficacy and the presence of neutralizing antibodies in some patients. None of the patients in the phase II Bristol trial had any neutralizing serum antibodies.

The license to recombinant GDNF subsequently was acquired by Medgenesis Therapeutix Inc., of Victoria, British Columbia, which supported the phase II trial in Bristol.

Gill attributes the failure of the Amgen study to poor drug delivery, saying most GDNF accumulated at the tip, or refluxed up, the catheter. "You need a high flow rate to fill the volume of the putamen," he said. "That's the problem we faced after the failure of the Amgen trial."

The system Gill devised in collaboration with U.K. engineering company Renishaw plc is being used by the Finnish company Herantis Pharma plc to deliver another growth factor, cerebral dopamine neurotrophic factor (CDNF), in a phase I safety trial. The study received a €6 million (US$6.8 million) grant from the EU's Horizon 2020 research funding program.

Pekka Simula, CEO of Herantis, told *BioWorld MedTech* the Bristol GDNF study has paved the way for the CDNF trial. "CDNF and GDNF are structurally and mechanistically completely different. They are very distinct as neurotrophic factors, but share the same challenge that they need to be delivered intracerebrally," he said.

Gill also has been using the delivery system in the treatment of children with the lethal brain cancer diffuse intrinsic pontine glioma. Although not a formal trial, he said overall survival has doubled.

The results of the phase II trial in Parkinson's disease are not as clear-cut as would have been desirable, but there are signs of promise, said Erich Mohr, chair and CEO of Medgenesis. "In particular, when the scores on three of the key assessments

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Fujirebio

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Inc., a Johnson & Johnson (J&J) company to develop an Amyloid Beta 42/40 RATIO assay to run on the Lumipulse G series equipment. Janssen expected to use the test to improve clinical assessment of its investigational oral BACE inhibitor, atabecestat. But J&J pulled the plug on the candidate later that same month on toxicity issues.

The field of drug development for Alzheimer's disease is littered with failures – despite widespread activity across a wide variety of pharmaceutical and biotech companies. Most recently in January, Roche discontinued a pair of phase III trials of anti-beta-amyloid candidate crenezumab in early, sporadic AD on disappointing interim data.

The Swiss pharma giant is not exiting AD entirely, though; the company is continuing phase III trials for gantenerumab and phase II testing for anti-tau molecule RG6100 – as well as working to further advance its imaging and fluid-based diagnostics.

More accurate and earlier-stage diagnostics are widely thought to be crucial to identifying patient populations that can benefit from investigational treatments – as well as to track disease progression and/or treatment effect. (See *BioWorld MedTech*, Aug. 14, 2018.)

Fujirebio is a consolidated subsidiary of Miraca Holdings Inc., which is publicly listed on the Tokyo Stock Exchange. It is based in Japan and specializes in IVD test development. It has acquired a series of international IVD companies over the years including Centocor Diagnostics in 1998, Canag Diagnostics in 2006 and Innogenetics in 2010.

"We are very pleased that the FDA has granted us breakthrough status for this important new diagnostic tool in the fight against Alzheimer's Disease," said Fujirebio President and CEO Monte Wiltse. "The entire Fujirebio group of companies are committed to bringing novel diagnostic tools for Alzheimer's disease to health care systems globally, and we look forward to working closely with the FDA to provide both physicians and patients this innovative, new test." ♦

Appointments and advancements

Anaconda Biomed SL of Barcelona has appointed Lieven Huysse to the position of chief medical officer and Jordi Cardona Vidal as the director of manufacturing. Huysse will lead the company's efforts to roll out clinical trial's for Anaconda's thrombectomy system for ischemic stroke, and previously served as senior director of medical affairs at Intrinsic Therapeutics Inc. Vidal will oversee scale-up of production of the thrombectomy device.

Integra Partners Inc., of New York has appointed Dominic Paniccia as the CEO effective March 31, succeeding Andrew Saltoun, who will stay with the company in the capacity of senior advisor. Paniccia joined the company in 2016 as Integra's inaugural chief financial officer, and has held management positions at American Express and AIG.

Tandem Diabetes Care Inc., of San Diego said the company's president and CEO, Kim Blickenstaff, will move to the new position of executive chairman of the board of directors. Taking over for Blickenstaff will be John Sheridan, who will move to the president and CEO job from the executive VP and chief operating officer position he has held since April 2013. Board chairman Dick Allen will shift to the position of lead independent director, and Tandem said Fred Cohen has decided he will not run for reelection to the board. Sheridan is expected to be nominated to take Cohen's place on the board, the company said.

Product briefs

Abbott Laboratories of Abbott Park, Ill., reported the availability of its latest rapid influenza diagnostic test (RIDT), Binaxnow Influenza A & B Card 2. The reformulated test has been granted waived status under the Clinical Laboratory Improvements Amendments (CLIA) by the U.S. FDA for use with Abbott's Dgival diagnostic reader (formerly Alere Reader) for the rapid detection of influenza virus. The combined platform is available for use in hospital laboratories, emergency rooms, physician offices, walk-in clinics and urgent care centers.

Baltimore-based **Eneura Inc.** has obtained a new 510(k) clearance from the U.S. FDA. This new marketing clearance expands the product indication of acute and preventive treatment of migraine to include children 12 years of age and older. The private company received clearance for acute and preventive treatment of migraine in adults in 2017. With this FDA clearance, the single-pulse Transcranial Magnetic Stimulation (sTMS) is now the only migraine product in the U.S. indicated both for the acute and prophylactic treatment of migraine headache in adults and children (12 years of age and older). The sTMS product induces a mild electric current that modulates nerve cells in the brain. This technology is believed to interrupt the brain hyperactivity associated with migraine. The expansion of the label to include children 12 years of age and older was supported, in part, by the FDA's review of Eneura's ESPOUSE study, which was conducted in adult patients at eight leading U.S. Headache Centers. Following a protocol of daily use, 46 pecent of patients reported at least a 50 percent reduction in headache attacks. There were no serious adverse events reported during the study.

Dublin-based **Medtronic plc** reported U.S. FDA 510(k) clearance of the Accurian RF ablation platform, which conducts radio frequency (RF) ablation of nerve tissues. RF ablation is a minimally invasive procedure in which current produced by radio waves heats up a small area of nerve tissue to stop it from sending pain signals, thereby reducing pain.

Tepha Inc., of Lexington Mass., initiated a pilot evaluation of its P4HB regenerative polymer scaffold for the surgical treatment of stress urinary incontinence (SUI). The study was initiated in Cape Town, South Africa in partnership with the Pelvic Floor Foundation of South Africa (PFFSA) and the University of Cape Town. The first procedures were performed by investigators, at the University of Cape Town and the Academic Medical Center, Amsterdam, Netherlands. The Cape Town SUI study represents the first clinical application of Tepha's P4HB polymer technology in the field of urogynecology. Patients in the study are being treated with a mid-urethral sling device based on Tepha's resorbable P4HB polymer. Unlike most currently available non-resorbable mid-urethral sling devices made from polypropylene, the Tepha P4HB regenerative scaffold has been designed to resorb and remodel to form a new natural tissue plane that will maintain continence and potentially minimize long term complications. The Cape Town pilot SUI study with the P4HB regenerative scaffold is primarily a safety and feasibility study that will include certain efficacy endpoints. The patients will be followed for two years during which time the P4HB scaffold is expected to completely resorb and remodel. Tepha is planning to initiate further clinical evaluation of its P4HB regenerative scaffold in Europe in 2019 and the U.S. in 2020.

Newton, Mass.-based **The Learning Corp**, published the first large scale retrospective study of post-stroke rehabilitation practices that compares outcomes among patients using tablet-based therapy at home and those who complete the same therapy in a clinic. The study, published in *Frontiers in Neurology*, analyzed data from 3,686 Constant Therapy users – patients with post-stroke aphasia – over a four year period (2013-2017). In the study, home users and clinic users completed cognitive and language tasks such as Functional Math, Name Pictures, Map Reading and Auditory Commands that are featured in the Constant Therapy app. Home users worked independently while clinic users worked under the guidance of a clinician. The study compared improvement rates for both groups, who were initially struggling with a task (less than 60 percent accuracy) but eventually mastered it (more than 90 percent accuracy). The results showed that home users took less time to master tasks than users who only practiced in the clinic. While both home and clinic users required roughly the same amount of practice to master cognitive and language tasks, users who had on-demand access to therapy on their tablet mastered tasks in a median of six days, while those with only in-clinic access mastered tasks in a median of 12 days.

GDNF

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are combined – motor response, activities of daily living and good quality on time – it reveals a highly significant difference between the treatment and placebo groups," he said.

This Parkinson's disease composite response is being championed by the patients' group European Parkinson's Disease Association, as a means to combine motor symptoms, non-motor symptoms and treatment-related complications, in a single disease rating score.

Mohr said he believes it may better capture the full effects of GDNF. "We're working to get it scientifically validated so that it can be used in future trials," he said.

Now Gill and Medgenesis need to raise £4 million (US$5.3 million) for the first stage of the phase III trial, treating 17 patients in each arm.

A year ago, Pfizer Inc. terminated an option it had with Medgenesis to license GDNF as a potential treatment for Parkinson's disease. "[The trial] was ready to roll, supported by Pfizer," Gill said. "Medgenesis was left stranded."

It is now a race against time to raise the money because existing supplies of GDNF expire in 2021. "The key thing is to get going before September," said Gill.

"Even at a low dose we have seen evidence of patient improvement, which is incredibly encouraging. Now we need to move towards a definitive clinical trial using higher doses, and this work urgently needs funding," he said. ♦

Regulatory front

The U.S. **FDA** reported the class I recall of the Lifepak 15 monitor/defibrillator made by **Physio-Control Inc.** of Redmond, Wash., due to the risk that the unit will freeze up after delivering a shock. The recall affects more than 8,100 units distributed in the U.S. between March 2013 and July 2016, and the FDA said the situation can be rectified only by restarting the device or by disconnecting and reconnecting the device to all power sources. Physio-Control is providing a firmware update to address the problem, and the FDA said the problem has resulted in serious injury, including death.

Health Quality Ontario (HQO) has endorsed the use of public funding for artificial disc replacement for degenerative disc disease of the cervical spine, decreeing the procedure is more effective than fusion and requires fewer follow-up procedures. The agency said patients had expressed a desire for more options and greater autonomy in medical decision-making. Disc replacement is said to best fusion for cost effectiveness for both one- and two-level degeneration, adding that the net budgetary impact over five years is likely to be roughly $916,000 for single-level procedures and $706,000 for two-level procedures. HQO also recommended the use of public funding for Internet-delivered cognitive behavioral therapy (iCBT) for mild to moderate depression, stating that iCBT outperforms "waiting list" for improvement of symptoms. The agency likewise recommended iCBT for anxiety disorders, stating that the annual costs would come to $10 million to $40 million for the depression indication and $16 million to $65 million a year for anxiety disorders. Ontario's Ministry of Health and Long-Term Care said it would take the both recommendations under advisement.

The U.K. **Medicines and Health Care Products Regulatory Agency** said a hard, no-deal Brexit would result in U.K.-based notified bodies losing the recognition of the European Medicines Agency for medical device marketing licenses. The agency said in its latest update that it would continue to recognize any certificates issued by British NBs after the March 29 Brexit date in the event of a no-deal Brexit, and that existing clinical trials would enjoy continued recognition. MHRA said that in the event of a hard Brexit, it would have a regulatory system in place as of March 30 that would "mirror all the key elements" in the European Union's regulations for devices and in vitro diagnostics.

Other news to note

Biocept Inc., of San Diego, will collaborate with Providence St. Joseph Health, Southern California, and its wholly owned affiliates Providence Saint John's Health Center and the John Wayne Cancer Institute, to conduct a study to validate the use of cerebrospinal fluid as a specimen type with Biocept's Target Selector liquid biopsy platform.

Caesarea, Israel-based **Itamar Medical Ltd.** will list and trade its American Depositary Shares (ADS) on the Nasdaq Capital Market under the ticker symbol "ITMR" on or about Feb. 27, through a level II ADS program.

Pangea Laboratory, of Costa Mesa, Calif., reported the licensing of a new urine-based laboratory developed test (LDT) for bladder cancer detection. Sold under the name Bladder Care, the test is noninvasive, cost-effective and epigenetic-based. Urine samples for the Bladder Care test can be collected at home or at the doctor's office and mailed to Pangea for analysis. Pangea conducted a preclinical collaborative study with Zymo Research, in which 182 urine samples were analyzed using the test. The cohort consisted of 97 urine specimens collected from bladder cancer patients and 85 healthy control samples. The study showed that Bladder Care has 93.8 percent sensitivity, 85.9 percent specificity, 88.4 percent positive predictive value and 92.4 percent negative predictive value.

Titan Pharmaceuticals Inc., of South San Francisco, reported the execution of a specialty pharmacy distribution and services agreement with Alliancerx Walgreens Prime that will expand patient access to treatment with Probuphine (buprenorphine) implant, Titan's six-month maintenance treatment for opioid use disorder in eligible patients.

Xsurgical, a Cambridge, Mass.-based firm developing and bringing to market a remotely controlled surgical robot, has been accepted for membership in the Medical Technology Enterprise Consortium, which is working with government agencies to foster integrated research partnerships to speed availability of medical technology solutions to the military, veterans and the civilian population.

Orthopedics Extra

Keeping you up to date on recent developments in orthopedics

By Holland Johnson, Executive Editor

Vitamin D and immune cells stimulate bone marrow disease

The bone marrow disease myelofibrosis is stimulated by excessive signaling from vitamin D and immune cells known as macrophages, reveals a Japanese research team. These findings could help to develop alternative treatments that do not target problem genes. The findings were published on Feb. 4, 2019, in the online edition of *Blood*. There are three types of blood cell: white blood cells, red blood cells, and platelets. All three types are created from hematopoietic stem cells located in the bone marrow. Myelofibrosis causes an abnormal increase in the cells that produce collagen fibers called fibroblasts. The bone marrow becomes filled with these fibers, preventing the body from producing blood cells as normal. This condition can make it hard to control other diseases, and bone hardening (osteosclerosis) also occurs. Myelofibrosis occurs in blood tumors called myeloproliferative neoplasms, which are caused by genetic mutations of hematopoietic stem cells. The study results show that pathological macrophages produced by vitamin D receptor signaling play an important role in the development of myelofibrosis. Clinical treatment uses inhibitors to target the causative genes of myeloproliferative tumors, but this is not always effective in treating myelofibrosis. The researchers said these new findings may help to develop a treatment method for the elderly targeting the vitamin D pathway and macrophages. The article is titled "Vitamin D receptor-mediated skewed differentiation of macrophages initiates myelofibrosis and subsequent osteosclerosis."

Diabetes-free donors are best source of stem cells for bone repair in type 1 patients

A groundbreaking study released today in *Stem Cells Translational Medicine* shows that the gold standard for obtaining stem cells to use in transplantation therapy – harvesting them from the patient himself – is not the best way to go when attempting to regenerate bone in a person with type 1 diabetes. While stem cell-derived exosomes have exhibited promise for bone regeneration, identifying an appropriate source to obtain them has proven difficult. Researchers at Shanghai Jiao Tong University Affiliated Sixth People's Hospital wanted to find out how exoxomes secreted by bone marrow mesenchymal stem cells (BMSCs)derived from type 1 diabetes rats (dBMSC-exos) measured up to those derived from normal rats (nBMSC-exos). "Our study indicated that both the nBMSC-exos and the dBMSC-exos had some regenerative effect, but the cells derived from the healthy animals were far more potent than those from the rats with diabetes," the researchers said. "We think this is because the components present in the BMSC-exos may have changed as a result of the diabetes." The next step will be to repeat the study using cells derived from humans. The article is titled "Impaired bone regenerative effect of exosomes derived from bone marrow mesenchymal stem cells in type 1 diabetes."

Ultrasound can assess bone health, increase early screening for osteoporosis

In a study that could lead to wide use of inexpensive ultrasound screenings for osteoporosis, researchers found data from ultrasonography of the calcaneus (heel bone) was equal to data gathered using dual-energy X-ray absorptiometry (DXA), which is considered the gold standard for assessing bone health. The findings could lead to lower costs and increased screening for populations at-risk for bone diseases, which study authors say extends well beyond postmenopausal women. Researchers at West Virginia School of Osteopathic Medicine said DXA scans remain the best option for thorough, comprehensive information on a patient's bone health. However, the equipment is expensive, immobile and exposes patients to ionizing radiation. Those limitations create barriers to screening larger populations. "Using ultrasound to scan the heel won't give us all the information we could gather with a full DXA scan," said Carolyn Komar, associate professor of biomedical sciences at West Virginia School of Osteopathic Medicine and coauthor on this study. "However, it gives us a clear enough snapshot to know whether we should be concerned for the patient." The article, titled "Advancing Methods of Assessing Bone Quality to Expand Screening for Osteoporosis," was published Feb. 25, 2019, in *The Journal of the American Osteopathic Association*.

New form of hereditary osteoporosis

A research group headed by Outi Mäkitie, University of Helsinki, Finland, identified in families with childhood-onset osteoporosis disease-causing mutations in a gene that had previously not been connected with the skeletal system or osteoporosis. The researchers said that mutations of the gene SGMS2 were identified as the cause of the disease. SGMS2 encodes an enzyme involved in sphingolipid metabolism; mutations lead to changes in the enzyme function and – through mechanisms so far partially unknown – a serious disturbance of bone metabolism and mineralization. Mutation carriers had, since childhood, suffered fractures in their limbs and spine even as a result of minor injuries. Certain study subjects also presented neurological symptoms, transient facial nerve paralysis being a particularly common one, which, according to Mäkitie, may be one of the distinctive features of this form of osteoporosis. The examination of bone samples collected from three patients demonstrated that their bone tissue differed from normal bone tissue: the number of bone cells was atypical and bone mineralization was disturbed. The changes were particularly clear in the cortical bone, the region with the most abundant expression of the SGMS2 gene. The researchers said this gene finding increases understanding of the mechanisms underlying osteoporosis and opens new avenues for the development of osteoporosis diagnostics and drug therapies. The article, published Feb. 19, 2019, in *JCI Insight*, is titled "Osteoporosis and skeletal dysplasia caused by pathogenic variants in SGMS2."