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COULD QUELL LIVER SHIVERS

A fungus among us: FDA adcom tempers Cempra, lefamulin affair starting?

By Randy Osborne, Staff Writer

Amesh Adalja, of the University of Pittsburgh School of Medicine, told *BioWorld Today* that, although too early to tell for sure about toxicity, it's "an encouraging sign" that Nabriva Therapeutics AG has chosen to develop lefamulin, a new antibiotic in the mushroom-derived pleuromutilin class that has shown a clean profile in phase II trials against skin infections.

"Other drug classes that may have been known for a while [should start] being commercially developed," Adalja said, as drugmakers "start looking for things that

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Expanding on SCOTUS patent decisions harmful to U.S. innovation

By Mari Serebrov, Regulatory Editor

Too many U.S. patent examiners aren't "getting the memo" on how to apply recent court rulings on laws of nature and abstract ideas to patent applications covering drugs and diagnostics to software and financial management tools.

That seemed to be the consensus

See Patents, page 4

REGULATORY

EMA opens process on new phase I trial rules, post Bial study death

By Cormac Sheridan, Staff Writer

DUBLIN – The EMA launched a formal consultation process Tuesday on the development of a new guideline for first-in-human and early stage clinical trials of investigational drugs.

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REGULATORY

HOTSPOT FOR EXPANSION

As regulations tighten, China health care sector draws global interest

By Carmen Ho, Staff Writer

HONG KONG – Biotech companies worldwide are gearing up to expand into the China market even as the CFDA toughens up its health care market

See China, page 6

EUROPE

EMA workshop focuses on big data opportunity in regulatory science

By Nuala Moran, Staff Writer

LONDON – Big data has the power to change the way drugs are accessed, used and regulated, but there are barriers to its implementation – in complying with data protection legislation, engendering trust, understanding the strengths and limitations of datasets and developing analytical methods to reach conclusions that can be transferred through to regulatory decisions.

"We need to have a reflection and see how we can jointly address and take advantage of [big] data," said Guido Rasi, executive director of the EMA, opening a workshop convened by the agency to identify opportunities for big data in drug development and regulatory science.

Electronic health data are being generated around millions of patients, providing an opening to better

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IN THIS ISSUE

THE BIOWORLD BIOME

T cells & tumors, revisited

By Anette Breindl, Senior Science Editor

Among the top news to come out of the 2016 meeting of the Society for the Immunotherapy of Cancer (SITC) last week was the fact that Keytruda (pembrolizumab, Merck & Co. Inc.) monotherapy in second-line or greater bladder cancer more than doubled overall survival compared to

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FINANCINGS

Beyondspring Pharmaceuticals Inc., of New York, filed an F-1 with the SEC seeking to raise up to $100 million, including overallotments, in an IPO. The company, incorporated in the Cayman Islands, filed as an emerging growth company under the Jumpstart Our Business Startups Act and applied to list its shares on Nasdaq under the ticker BYSI. In its filing, Beyondspring said proceeds will be used to fund separate phase II/III trials of lead compound, plinabulin, in combination with docetaxel and with other chemotherapeutic agents to treat docetaxel chemotherapy-induced severe neutropenia and to prevent non-docetaxel chemotherapy-induced severe neutropenia; to conduct a phase III trial of plinabulin in combination with Opdivo (nivolumab, Bristol-Myers Squibb Co.) to treat non-small-cell lung cancer (NSCLC); to support development of plinabulin in NSCLC patients with KRAS mutations; to conduct preclinical and early clinical studies of follow-on candidates BPI-002 and BPI-003; and to fund research collaborations and other company expenses. Citigroup, Guggenheim Securities, FBR Capital Markets and China Renaissance are joint bookrunners on the offering, which was not priced. (See *BioWorld Today*, March 18, 2015.)

Immune Therapeutics Inc., of Orlando, Fla., said it redeemed a $656,250 convertible note issued to JMJ Financial. The company said its cost of capital is decreasing and it is seeking to restructure and strengthen its balance sheet by year-end.

Synthetic Biologics Inc., of Rockville, Md., priced an underwritten public offering of 25 million common shares and warrants to purchase an additional 50 million common shares at $1 per unit. The price represented a discount of 30 percent to Monday's close of $1.43 for the company's shares (NYSEMKT:SYN). The offering generated gross proceeds of $25 million. If exercised in full, the warrants could result in additional net proceeds of $78.8 million. The company provided the underwriter a 30-day option to purchase up to 3.75 million additional common shares and warrants to purchase up to 7.5 million additional shares. Cantor Fitzgerald & Co. is acting as sole book-running manager. On Tuesday, the company's shares fell 54 cents to close at 89 cents. (See *BioWorld Today*, Dec. 4, 2015.)

Tesaro Inc., of Waltham, Mass., priced an underwritten public offering of 1.75 million common shares at $135 apiece, a discount of 9 percent to Monday's close of $148.50 for the company's shares (NASDAQ:TSRO). The offering is expected to raise approximately $236.3 million, and Tesaro granted underwriters an option to purchase up to 262,500 additional common shares, potentially adding about $35.4 million to the raise. The company said it expects net proceeds of about $224.1 million from the offering. Citigroup, Leerink Partners, Credit Suisse and Wells Fargo Securities are bookrunners, with Baird, FBR, Guggenheim Securities, Raymond James, Suntrust Robinson Humphrey and Wedbush Pacgrow as co-managers. On Tuesday, the company's shares closed at $131.04 for a loss of $17.46, or 11.8 percent. (See *BioWorld Today*, Oct. 11, 2016.)

OTHER NEWS TO NOTE

Albireo Pharma Inc., of Boston, said lead candidate A4250 was granted access to the EMA's Priority Medicines, or PRIME, program for the treatment of progressive familial intrahepatic cholestasis, or PFIC.

Centrexion Therapeutics Inc., of Baltimore, said the FDA granted fast track designation to CNTX-4975 to treat Morton's neuroma, a rare nerve disorder in the foot. The company completed a phase IIb study in patients with the condition, and an open-label, multiple-dose extension study is ongoing. (See *BioWorld Today*, March 31, 2016.)

Cynata Therapeutics Ltd., of Melbourne, Australia, said it received an R&D tax incentive refund from the Australian government of approximately A$1.75 million (US$1.3 million) for the 2015-16 financial year.

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BUSINESS OFFICE

Donald R. Johnston (Senior Director, Current Awareness), Penney Holland (Web Production Manager)

CONTACT US

Jennifer Boggs, (770) 810-3120 // Anette Breindl, (770) 810-3134 // Michael Fitzhugh, (770) 810-3064 // Penney Holland, (770) 810-3047 // Donald R. Johnston, (770) 810-3118 // Nuala Moran, 44-7778-868-579 // Randy Osborne, (770) 810-3139 // Marie Powers, (770) 810-3136 // Mari Serebrov, (770) 810-3141 // Cormac Sheridan, 353-87-6864323 // Peter Winter, (770) 810-3142 // Lynn Yoffee, (770) 810-3123

Nabriva

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might be on the shelf or other classes, really aggressively going after some of the other candidates that they haven't pursued in the past."

Companies have been more focused on chronic and lifestyle therapies because "a drug that someone is going to be on for the rest of their life is a lot more attractive to them than antibiotics," Adalja added. Meanwhile, resistance grows.

Liver toxicity worries in last week's FDA advisory panel on Cempra Inc.'s solithromycin added more weight to the optimism around the pleuromutilin candidate from Nabriva, of Vienna. The FDA's Antimicrobial Drugs Advisory Committee evaluated Chapel Hill, N.C.-based Cempra's oral and injectable forms of solithromycin and voted 13-0 in favor of efficacy in community-acquired bacterial pneumonia (CABP), but the panel split on the benefit/risk profile question, balloting 7-6. In briefing documents and during the panel meeting itself, solithromycin – in the macrolide class and ketolide subclass – was haunted by Ketek (telithromycin), the first ketolide antibiotic approved (in 2004) for CABP, which Sanofi SA, of Paris, pulled from the market after a boxed warning and restricted label were added. (See *BioWorld Today*, Oct. 30, 2006, Nov. 3, 2016, and Nov. 7, 2016.)

PDUFA dates are Dec. 27 and Dec. 28 for the two forms of Cempra's solithromycin.

Nabriva's compound has shown in vitro activity against the most common pathogens associated with CABP, including multidrug-resistant strains. With a special protocol assessment from the FDA in hand, Nabriva began its two-trial phase III program with lefamulin, being tested as an intravenous (I.V.) and oral therapy. RBC Capital Markets analyst Adnan Butt about a year ago noted that lefamulin has been shown noninferior to vancomycin in patients with acute bacterial skin and skin structure infections, proving effective while turning up no safety signals such as QTc interval prolongation. He started coverage with an "outperform" rating and a $21 price target. Nabriva, which said Friday it was in the process of raising capital through a rights offering, closed Tuesday (NASDAQ:NBRV) at $4.44, down 54 cents, or 10.8 percent.

Lefamulin is derived from the fungi *Pleuro mutilis*, and works by inhibiting bacterial protein synthesis at two unique binding sites on the ribosome, thus yielding early stage efficacy against pathogens that have evolved resistance to widely used classes of antibiotics such as macrolides, quinolones and tetracyclines. London-based Glaxosmithkline plc in 2007 won approval of a topical antibiotic in the class for impetigo, Altabax (retapamulin), but no systemic pleuromutilin has been cleared for marketing.

STAVING OFF A CRISIS

In a research report after the Cempra panel meeting, RBC's Butt acknowledged phase II studies with lefamulin in the skin infections turned up "isolated increases in alanine and aspartate aminotransferases; however, they were comparable among treatment groups, which included low- and high-dose lefamulin and vancomycin." For the "entirely new mechanism from a new drug class, liver-damage concerns do not appear to be an issue at this time." Overall, he said, "The value proposition for Nabriva's lefamulin is at least as attractive as if not better than Cempra's solithromycin. While Cempra's phase III program in CABP (less severe patients) is completed, Nabriva's phase III trials still have to read out," and shares of the latter may be due for a boost when they do, he said.

Leerink analyst Paul Matteis likes lefamulin's odds, too. LEAP1, the phase III I.V.-to-oral CABP study, already underway, has been amended upon an agreement with the FDA reached in April. The change means regulators will now allow for a 12.5 percent noninferiority margin (compared to moxifloxacin ± linezolid) as opposed to the original 10 percent margin, along with treatment to seven days as opposed to five days, "both reflecting FDA recognition of the difficulty of performing I.V.-to-oral studies and the severity of the patients treated. With the amendment, LEAP1 can enroll a minimum of 550 patients with 90 percent power to hit the FDA endpoint of early clinical response and the EMA endpoint retains 80 percent powering for test of cure." An interim analysis due in the fourth quarter of this year "will assess if statistical assumptions remain valid," he said.

The LEAP2 trial, begun in April, is testing an oral-only lefamulin regimen and will enroll 740 patients with a 10 percent noninferiority margin (compared to moxifloxacin) for the primary efficacy endpoint, reflecting the fact that patients will be less severe than those recruited to LEAP1.

"Any new antibiotic in this situation is a major advance, because we are in dire straits with regard to antibiotic-resistant bacteria," Adalja said. "We are really scrambling to find new antibiotic solutions" in order to "stave off what really is going to be a crisis."

Nabriva was incorporated as a spin-off from Sandoz GmbH (now part of Basel, Switzerland-based Novartis AG) and started operating in February 2006. Backers include Vivo Capital, HBM Healthcare Investments, Orbimed Healthcare Fund Management, Phase4 Partners, Omega Funds, Wellcome Trust, Ecor1 Capital, Novartis Venture Fund and Boxer Capital. The firm also has an office in King of Prussia, Pa. //

Patents

Continued from page 1

Monday as speaker after speaker at a U.S. Patent and Trademark Office (PTO) roundtable on patent eligibility praised the PTO for issuing timely, informative guidance memos on how it will implement new precedential judicial decisions, but said many examiners are going beyond the courts in rejecting applications on basic 101 eligibility criteria.

"The memos are good, but probably not being followed," patent attorney Robert Sachs said.

Instead of applying the court's reasoning, many examiners assume that any claim citing a law of nature, a naturally occurring phenomenon or an abstract idea – the exceptions listed under Section 101, the threshold for patent eligibility – cannot be patented regardless of what else they cite. As a result, the PTO has expanded and broadened what falls into the not-patentable category.

"It's not the examiner's job to add to the list" of exceptions, as that's a judicial function, not an administrative one, Sachs said.

Because of the PTO's ineligibility assumption, "101 rejection has become an insurmountable barrier," said Barbara Fiacco, second vice president of the American Intellectual Property Law Association's board.

Patent attorney Denise Kettelberger agreed. "101 rejections are clearly eating our lunch," she said, adding that patents for life sciences inventions are a big target, because every claim is likely to have a correlation to a natural law.

The problems stem from Supreme Court decisions in *Mayo* and *Myriad*, which concern the eligibility of diagnostic claims linked to naturally occurring blood metabolite levels and genetic mutations, as well as *Alice*, a case involving computer-implemented inventions in which the high court set forth a test for evaluating the subject matter eligibility of patent claims. (See *BioWorld Today*, March 21, 2012, and June 14, 2013.)

SORTING OUT THE CONTOURS

In deciding those cases, the Supreme Court blurred and expanded the boundaries for 101 patent exceptions. Ever since, the U.S. Court of Appeals for the Federal Circuit has been left to interpret those decisions and "sort out the contours of 101," Kettelberger said.

Meanwhile, the PTO has tried to implement both the decisions and the contours through guidance and training examples that address claims in multiple technology areas, including nature-based products and inventions concerning abstract ideas, PTO Director Michelle Lee said in opening the roundtable.

The most recent examples, released in May, cover technological fields in the life sciences arena "specifically requested by the public, such as vaccines and diagnostics, which have not been directly addressed by the courts," Lee said. The examples showed ways such claims could be drafted for eligibility.

But changes in how claims for complex drugs and devices are drafted to design around 101 issues could make a safe, effective product useless or dangerous, Kettelberger pointed out. She added that her hope is that the 101 issues will go away as the "Federal Circuit continues to do its thing."

Warren Woessner, who works with startups and universities on patenting their inventions, said a split on the Federal Circuit might be needed to force the Supreme Court to rethink its decisions, which have been especially hard on diagnostics. "We want the Supreme Court to somehow fix things – to take *Mayo* back," he said.

So far, the Federal Circuit has been unified in applying the high court's decisions, but a few judges have gone along grudgingly. Woessner noted that when the appellate court invalidated a method patent last year protecting Sequenom Inc.'s MaterniT21, a noninvasive test that revolutionized prenatal diagnoses for conditions such as Down's syndrome, one of the judges basically said "*Mayo* made me do it" in his concurring opinion.

When the Federal Circuit subsequently denied Sequenom's request for an en banc hearing, two of the judges expressed concern that, as a result of *Mayo*, a lot of damage has been done to diagnostic patents. Despite those concerns and the harm its ruling has caused, the Supreme Court refused to hear Sequenom's appeal. (See *BioWorld Today*, Dec. 4, 2015.)

Several speakers at the roundtable addressed the problem with diagnostic patents in particular. Patent attorney David Gass said that while diagnostics are directed to laws of nature, they don't prevent innovation. Instead, they promote it. He also pointed out that the steps taken with a diagnostic occur in the lab, not in the patient.

Benjamin Jackson, of Myriad Genetics Inc., said broadly excluding molecular diagnostics from patent protection is unwise from a policy perspective, because they are the gateway to precision medicine. In taking such a broad view of the laws of nature that would strip molecular diagnostics of patent protection, the PTO confuses statistical correlation with a direct causal/mechanistic link. "Correlation does not equal causation," Jackson said. It can hint at causation, but it doesn't prove it.

Molecular diagnostics look at a complex web of natural laws. Determining such statistical links to disease is very different from identifying a biological marker in the blood, he explained.

NEED FOR EXAMINER TRAINING

Other problems that came up repeatedly at the roundtable spoke directly to lack of examiner training – boiler plate 101 rejections, patents being denied based on just a few words in the claims, lack of meaningful engagement, use of nonprecedential court decisions and unrelated cases, examiners not being empowered to make 101 decisions, and inconsistencies in 101 decisions from examiner to examiner and across the centers. One patent attorney said he gives copies of

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Trials

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The agency published a draft guideline, to which it is inviting responses from interested parties by Feb. 28, 2017. It aims to publish a final version during the first half of 2017. That would then form the basis of a new approach to the conduct of phase I and early stage trials – failure to follow them could compromise a drug developer's application for approval.

"Scientific guidelines reflect a harmonized approach of the EU member states and the agency on how to interpret and apply the requirements for the demonstration of quality, safety and efficacy set out in the community directives," an EMA spokeswoman told *BioWorld Today*. "The agency strongly encourages applicants and marketing authorization holders to follow these guidelines. Applicants need to justify deviations from guidelines fully in their applications at the time of submission."

The move is part of the London-based EMA's formal response to the fiasco that occurred at a Biotrial Research SAS clinical research facility in Rennes, France, last January, when one volunteer, 49-year-old father of four Guillaume Molinet died and five others suffered neurological injuries during a phase I trial of BIA10-2474. Porto, Portugal-based Bial Portela & CA had been developing the compound, which it described as an oral fatty acid amide hydrolase (FAAH) inhibitor, for treating neuropathic pain. (See *BioWorld Today*, Jan. 20, 2016.)

Although not directly involved in sanctioning the trial – its oversight was the responsibility of the French regulator L'Agence nationale de sécurité du médicament et des produits de santé (ANSM) – the EMA started a formal review of its guidelines in first-in-man trials in May. A concept paper, which it published in July, noted that the existing guideline, which dates back to 2007, focuses mainly on the nonclinical aspects of drug development, such as animal toxicology testing, and on single ascending-dose trial designs.

The review is intended to reflect both the lessons learned from the Bial fiasco and the evolution in trial design that has occurred during the past decade. (The last revision occurred in the wake of the disastrous Tegenero trial of TGN1412 in London). First-in-man trials are now increasingly complex and include both single and multiple ascending-dose phases, food interaction studies and assessment of the investigational compounds effects in subjects of different age, for example.

The draft guidance proposes extending the nonclinical aspects of the guideline to better integrate nonclinical pharmacology and toxicology data into an overall risk assessment for first-in-human and early stage trials. It seeks to include the extrapolation and verification of the assumptions made in translating nonclinical data to the human setting and to expand on the so-called Mabel approach to analyzing the minimum anticipated biological effect level of a drug.

"Guidance is also provided on clinical aspects, including criteria to stop a study, the rolling review of emerging data with special reference to safety information for trial participants, and the handling of adverse events in relation to stopping rules and rules guiding progress to the next dosing level," the spokeswoman stated.

LESSON LEARNED?

The dust has by no means settled on the Bial case, meanwhile. Last month, lawyers acting on behalf of Rennes-based Biotrial issued a statement condemning "a campaign of denigration" orchestrated by the French newspaper *Le Figaro*, which is critical of the continued operation of Biotrial's Rennes facility. Although reports into the trial from two French agencies, ANSM and the social affairs directorate IGAS (Inspection générale des affaires sociales), concluded that the trial protocols were administered and followed appropriately, the English version of the IGAS report makes for grim reading.

BIA10-2474's structure did not set any alarm bells ringing, but its affinity and specificity for its supposed target were so weak that calling it an FAAH inhibitor is scientifically questionable. It had just micromolar levels of affinity for human FAAH. Inhibitors that other firms tested, including Pfizer Inc., had nanomolar affinity for human FAAH and far less affinity for other human hydrolases.

Pfizer, moreover, tested its compound, PF-04457845, against 68 receptors and a panel of 20 hydrolases, whereas Bial tested BIA10-2474 and one of its metabolites against just three serine hydrolases and five other enzymes. Johnson & Johnson, similar to Pfizer, was rigorous in its testing of its compound, JNJ-42165279. The FDA, drawing on data supplied by the EMA and the ANSM, concluded in August that BIA10-2474 "exhibits a unique toxicity that does not extend to other drugs in the class."

What had potential as a poorly performing me-too drug ended up taking the life of a healthy volunteer. Ten years on from the Tegenero fiasco, it is clear that not all of the lessons learned in that case were fully absorbed. It is impossible to state with any confidence that this time will be different. //

OTHER NEWS TO NOTE

Da Volterra, of Paris, said it joined the European Consortium COMBACTE-NET (Combatting Bacterial Resistance in Europe) alongside Medimmune, a unit of **Astrazeneca plc**, of London, and **The Medicines Co.**, of Parsippany, N.J. The consortium was established by the European Commission and the European Federation of Pharmaceutical Industries and Associations within the framework of the Innovative Medicines Initiative (IMI) to execute trials enabling the registration of therapeutic agents to treat antibiotic-resistant bacterial infections. Within the IMI framework, Da Volterra is launching an epidemiological study on 1,000 patients recruited in 30 European centers, who will be followed over three months to detect any occurrence of *Clostridium difficile* infections following antibiotic treatment and to discern populations for which preventing the pathology are most effective. A therapeutic solution, designated as DAV132, aims to prevent *C. difficile* infections in those high-risk patients.

China

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through a series of reforms.

"China remains one of the most compelling markets for life sciences and pharmaceutical companies globally," said Norbert Meyring, head of life sciences at KPMG China, a global advisory company. "This translates to opportunities for multinational pharmaceutical companies, which are currently unmatched by their local counterparts in both size and sophistication," he said. "The pharmaceutical industry is in a dynamic environment where China is trying to position itself not only as a vast and unique market, but also as a source and destination for high-quality research and manufacturing."

The International Pharmaceutical Federation (FIP) and the Chinese Pharmaceutical Association agreed to continue enhancing communication and promoting cooperation. Carmen Peña, president of FIP, and Sun Xianze, vice minister of the CFDA, met during the Global Conference on Pharmacy and Pharmaceutical Sciences Education, held in Nanjing, China, this month.

The conference gathered pharma industry leaders from across the world to set new goals for education and work force development of pharmacists and pharmaceutical scientists. Jointly hosted by FIP and the CFDA, it aimed to create a global vision for transformative health care and pharmaceutical sciences education. The platform enabled a dialogue among policymakers, education leaders and regulators to reach a consensus on how pharmaceutical competence and safety can be ensured.

China recently launched a drug supervision reform, which Sun introduced during the Global Conference. The reform includes a sharing system that publishes information on blacklisted drug and medical companies, among other businesses involved with food and drug safety.

The CFDA has also been cracking down on pharmaceutical companies, targeting subpar data in drug registration applications. Last month saw a rejection of 30 new drug applications, and 11 clinical trial institutions and contract research organizations suspected of providing fraudulent data have been investigated. (See *BioWorld Today*, Sept. 21, 2016.)

In May, the CFDA issued two announcements about quality and efficacy requirements for generics, including a review procedure and a list of generics that need to be reviewed by 2018.

In July, the CFDA issued a revised version of the Measures for the Administration of Drug Registration, which had not been updated since 2007. According to the draft, drugs that are not proved to have significantly better clinical value than biopharmaceutical products already available in China cannot be registered.

'VERY POSITIVE FOR BOTH SIDES'

FIP introduced a roadmap for advancing education and training through a shared vision to take on full responsibility and accountability for improving global health.

"The general direction of the government is to cut down on low-quality generics, and at the same time, simplify the process for innovative drugs," said Shi Lichen, director of the Dingchen Pharmaceutical Management Consulting Center.

"It is clear that strong action is needed. Forty [million] to 50 million new health workers, including pharmacists, will be needed globally. Around the world, ministers, their governments and all other stakeholders are expected to act," noted Philip Schneider, co-chair of the Global Conference on Pharmacy and Pharmaceutical Sciences Education.

While the tightening of policies in China's health care sector is causing headaches for a lot of existing players in the market that are not used to the new rigorousness, international companies looking to expand in China see this as an opportunity.

"The government is committed to increasing health care expenditure to meet the demands of an aging and increasingly affluent citizenry. It has also demonstrated a willingness to open up the sector to market forces, which will mostly benefit multinationals as they remain at the vanguard of some of the most innovative developments in the health care sector," said Meyring.

"I see the Chinese government working very hard to improve the accessibility and quality of health care for people in China, and this provides an exciting opportunity for serious health care providers, no matter in terms of clinical care, med tech or pharmaceuticals," Sigal Atzmon, CEO of Medix Group, told *BioWorld Today*. Medix is an international medical management company that links patients with specialists to enable interdisciplinary consultations and comprehensive treatments.

Medix currently has offices in Tel Aviv, London and Hong Kong but is eyeing the Mainland China market for its next expansion. The company has already worked with patients and health care professionals in Mainland China; the success of those cases and the evident demand has been highly encouraging, according to Atzmon.

"I think the government is doing right in being a bit more strict, and I think the discipline and strictness in China has done China very well," she added.

Atzmon said she sees a trend of foreign companies entering China and collaborating with local companies, creating a win-win situation for those determined to develop a competitive edge in the new regulatory environment.

"I think for the international companies, it takes time to understand the Chinese market well. And if they collaborate, if there is a strong, growing market of local startups, then it's very positive for both sides, because it's an ecosystem that can learn from each other," she said. **//**

Big data

Continued from page 1

understand disease and track the safety of drugs. Meanwhile, through genomics it is now known that cancers have lots of subsets, calling for a more personalized approach and raising the prospect of diagnosing earlier and treating earlier.

At the same time, social media and smart devices are making it possible to incorporate the needs, will and opinions of patients into regulatory oversight.

The sum of big data "will enable us to make better informed decisions," Rasi said.

The FDA is at the same stage as the EMA in coming to terms with big data, according to the agency's David Martin. "We are asking for inputs, but also having to deal with big data from day-to-day," he said.

The biggest impact to date has been in the establishment of the FDA's Sentinel system for assessing drug safety signals. From its inception in 2008, the system has grown to include data on 200 million people, and it is used for monitoring the safety of approved drugs.

An example of how the information has been used in practice concerns the new-generation oral anticoagulant Pradaxa (dabigatran), which was expected to reduce incidences of bleeding compared to warfarin. However, following its approval by the FDA in 2010, adverse event reports seemed to imply dabigatran-treated patients were more likely to suffer bleeding episodes than those treated with warfarin.

Bleeds are such a common side effect of warfarin the likelihood is they are rarely reported. Analyzing Sentinel data it was possible to say there was no higher risk of bleeds with Pradaxa, avoiding the need for a long-term epidemiological study.

Over the next five years, the FDA is planning a push on big data, including public workshops and more pilot studies. "These are early days for us, too," Martin said.

Patients also recognize the value of big data, according to Jean Georges, of the patients' group Alzheimer's Europe. His own organization has contributed to three EU projects harnessing big data to inform Alzheimer's research.

The most recent project, launched at the start of November, will pull together real-world data on Alzheimer's patients held in 75 separate national databases, with the aim of performing analyses to better inform regulators and help to elucidate biological mechanisms and pathways driving neurodegeneration.

"We have got feedback from patients and their carers living with the disease. They are recognizing the sharing of data is of vital importance," Georges said.

There also are challenges, of ensuring informed consent for use and re-use of data, data privacy and disclosure of data. "Therefore, governance is of great interest to patients and patients' organizations," said Georges. "We must be involved in discussion on the use of big data."

THE BIG DATA LANDSCAPE

If there is broad understanding of the potential of big data in drug development and regulation, it is another thing to marshal that resource, noted Lisa Latts, deputy chief health officer at IBM Watson, the computer company's machine learning arm.

It is "humanly impossible" to stay on top of the volume of data, with 100,000 clinical trials in progress at any one time, a further 1.8 million papers added to the repository of 424 million articles in the Medline database each year and the amount of data in electronic health records doubling every 24 months.

IBM's Watson system can analyze those huge amounts of structured and unstructured data to provide cognitive insights, learning and improving as more data are added to the mountain.

As one example of how that is being applied, at the beginning of the month, IBM announced a collaboration with Celgene Corp. to use big data to enhance pharmacovigilance and create an outcomes- and evidence-based drug safety decision support system for pharma companies.

The project will involve the collection, collation and automated analysis of data from sources including clinical trials, medical literature, regulators, social media and claims databases.

The result will be better management and interpretation of Individual Case Safety Reports, and improvements in picking up safety signals across a drug's lifecycle.

Similarly, Nico Gaviola, business manager at Google, described how the company is applying lessons learned from searches carried out via its internet browser to big data in health care.

Around one in 20, or 60,000 searches per minute on Google, relate to health. Now, the company is establishing a service that will enable users to apply machine-learning tools to search. Rather than a list of 273 million hits on searching "diabetes" it will be possible to analyze the information therein.

"We will provide all the infrastructure, storage, access and tools to be able to do Google-type searches for a few dollars – there will be no investment in systems or developing applications," Gaviola said.

Google intends to extend the service beyond publicly available information, to curate and manage proprietary data on behalf of clients.

REGULATORS, COMPANIES FACE BIG DATA DISRUPTION

Regulators "should be aware of the need to roll their sleeves up," said Luca Pani, director general of the Italian regulator AIFA. In the future, the majority of data "won't come from clinical trials," and given that, regulatory agencies must establish "which data and when" they will factor in when deciding on marketing authorizations.

In addition, the EMA cannot continue to operate at a European level, but has to link to the FDA, to the PMDA in Japan and

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T cells

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investigators' choice of standard chemotherapy agents.

Importantly, the benefit was seen regardless of PD-L1 expression levels, again reinforcing that though Keytruda and several other drugs work by blocking PD-1/PD-L1 signaling, their effectiveness is not determined in any simple way by the amount of target that is present on T cells.

Studies published in the Nov. 11, 2016, online issue of the *Proceedings of the National Academy of Sciences* have given new insights into the relationship among PD-1/PD-L1 expression, inflammation and other factors that determine the immune response to tumors, and to tumor immunotherapy.

Researchers from the University of Chicago investigated the T-cell-inflamed gene signature, in order to understand why that signature correlates with immunotherapy success. In many cases, T cells fail to infiltrate tumors, which leaves them unable to mount an antitumor immune response even after checkpoint blockade. One reason that has been proposed for that failure is that noninflamed tumors may present fewer antigens, but the Chicago group found "no correlation between gene expression and mutational burden in any cancer type" when they investigated the Cancer Genome Atlas data on all solid tumors. Instead, focusing on melanoma, they showed that in tumors that were not infiltrated, there was a lack of a particular immune cell type, namely Batf3-lineage dendritic cells. "Our data suggest that strategies to restore T-cell entry into noninflamed tumors should be developed," the authors concluded.

A team from Johns Hopkins University, meanwhile, has looked more broadly at the relationship among PD-1/PD-L1 expression, an inflammatory gene signature, mutational load and other checkpoint molecules in nine tumor types, also using data from the Cancer Genome Atlas. Echoing clinical findings that the relationship of PD-L1 expression to checkpoint blockade differs between tumor types, they found that the expression of PD-L2, a related checkpoint molecule, was "more closely related to an ongoing host immune response in certain tumor types than PD-L1." Like the Chicago team, they did not find a correlation between mutational load and inflammation in any tumor type they examined.

Collectively, the studies suggest that predictive and prognostic biomarkers for immunotherapy will depend on individual tumor types. But they also offer hope that tumors with low mutational burdens, too, can be successfully targeted with immuno-oncology approaches.

Editor's note: This is an outtake from BioWorld's Bench Press, a weekly feature that takes a look at translational medicine. Look for the attachment every Monday morning, or visit BioWorld's dedicated science portal, The BioWorld Biome: Our Habitat for All Things Science at www.bioworld.com.

OTHER NEWS TO NOTE

Juniper Pharmaceuticals Inc., of Boston, inked an agreement with **Allergan plc**, of Dublin, to monetize future royalty payments for U.S. sales of Crinone (progesterone gel). Under the agreement, Juniper will receive a one-time payment of $11 million from Allergan. Juniper sold U.S. rights to Crinone to Allergan in July 2010 and has since received a 10 percent royalty on U.S. sales. Juniper will continue to supply Crinone exclusively for all ex-U.S. markets and to receive revenue from those sales from **Merck KGaA**, of Darmstadt, Germany, which holds the product's marketing authorization in more than 90 countries. Crinone is indicated as part of assisted reproductive technology treatment for infertile women with progesterone deficiency.

Kamada Ltd., of Ness Ziona, Israel, signed a collaboration agreement with Yissum Research Development Co. of the Hebrew University of Jerusalem for the development of a eukaryotic expression system for recombinant human alpha 1 antitrypsin (AAT), an effort focused on maximizing protein yields and functionality. Upon completion of the work with Yissum, Kamada intends to begin GMP manufacturing scale-up activities. The main advantage of recombinant AAT over the plasma-derived AAT at the heart of Kamada's flagship product, Glassia, is its potentially higher availability at lower price per raw material, the company has said.

Marinus Pharmaceuticals Inc., of Radnor, Pa., disclosed preclinical data showing that the combination of its central nervous system-selective GABAA modulator, ganaxolone, plus diazepam administered intravenously (I.V.) produced a synergistic effect in blocking pilocarpine-induced seizures in a benzodiazepine-refractory model of status epilepticus (SE). Marinus is developing ganaxolone I.V. for the condition, a life-threatening medical emergency associated with high mortality and limited treatment options. The data were presented during a poster presentation at Neuroscience 2016 in San Diego. Subtherapeutic doses of diazepam and ganaxolone when administered in combination 15 minutes after onset of status epilepticus produced a partial or complete block of treatment-resistant status epilepticus in a rat model of SE, a clinically translatable model of that condition, the company said.

Midatech Pharma plc, of Oxford, U.K., selected its wholly owned candidate, MTR104, to take into a formal investigational new drug application-enabling program during 2017, followed by clinical trials planned for 2018. The program, which employs a nanoparticle-based conjugate, is focused on advanced liver cancer. (See *BioWorld Today*, Nov. 26, 2014.)

Neovacs SA, of Paris, acquired from Pilar, Argentina-based **Amegabiotech** a manufacturing license for interferon-alpha, a key component of Neovacs' lead therapeutic candidate, IFN-alpha Kinoid, which is composed of inactivated IFN-alpha coupled with a carrier protein, keyhole limpet hemocyanin. Financial terms of the license were not disclosed.

Big data

Continued from page 7

others. "These data are absolutely global," Pani said.

The pharma industry has made a "declaration of intent" to use big data and is putting a large amount of money into relevant research, according to Richard Bergstrom, director general of the European Federation of Pharmaceutical Industries and Associations (EFPIA).

There is "a lot of nervousness," in particular because technology companies are moving into pharma territory, and there are fears of the disruptive effects.

However, Bergstrom noted, it is also possible for the sector to change from within, and EFPIA members have shown they are willing to work together to deploy big data.

Changes in consumer demand and consumer behavior mean pharma will no longer be in control of all the knowledge about its products. "We have to relate to this, and the same is true for regulators," Bergstrom said.

Pharma and health care is behind on the digitization curve. It is a very regulated sector, and that has isolated it from its counterparts. "Big data is going to change that," Bergstrom predicted. "A common focus on outcomes can really make a difference. For industry, we will get paid for outcomes, not for pills."

CEOs of EFPIA member companies are frustrated that data on outcomes to demonstrate value are not available as yet. EFPIA is working with academics and clinicians to address that in Bigdata4bigoutcomes, a project to design standardized outcome measures that can be used to demonstrate value; increase access to outcomes data; and use big data to drive better delivery of health care. //

Patents

Continued from page 4

PTO guidance to examiners to make sure they understand what they're supposed to do.

Yet Lee insisted, "Each time we've updated our eligibility guidance, we provided comprehensive training for our examiners. After the most recent update in May, we conducted workshop training for the entire corps on how to perform the eligibility analysis, formulate eligibility rejections that clearly inform applicants of the reasons for the rejection, and evaluate and respond to applicant arguments on eligibility issues."

One area that hasn't had that training yet is the business methods unit. The PTO is in the process of developing new guidance and examples to help business method examiners apply the Supreme Court's 101 eligibility test to inventions in that area, Lee said. Comments made at the roundtable and an ongoing public comment period will be used in drafting the guidance and examples.

The PTO got an earful of comments about the business method unit at the roundtable, as it was singled out as having the poorest track record when it comes to 101 decisions. Patent attorney Sameer Vadera said 10 percent to 25 percent of other PTO office actions are rejections on 101 grounds, but the majority of applications going through the business methods unit are rejected for 101. He noted that many applications, including those for medical devices, are being examined as business methods.

Such misclassification and the low allowance rate discourages R&D and patent applications, Vadera said. He asked why anyone would spend $2 million to improve a hospital system if the technology won't receive patent protection.

Bob Stoll, a former patent commissioner, said that in narrowing 101 eligibility, patent examiners are weakening the patent system and hurting U.S. innovation. The impact is already being felt, he added, as patents that were denied in the U.S. are being approved in China and the EU. //

AMERICAN HEART ASSOCIATION 2016

The following data were presented at the American Heart Association Scientific Sessions 2016 in New Orleans.

Akcea Therapeutics Inc., of Cambridge, Mass., a wholly owned subsidiary of Ionis Pharmaceuticals Inc., presented results from an interim analysis of a phase I/IIa study of IONIS-ANGPTL3-LRx, showing that subjects with elevated triglycerides achieved substantial and statistically significant mean reductions in angiopoietin-like 3, or ANGPTL3, triglycerides and LDL-cholesterol of up to 83 percent, 66 percent and 35 percent, respectively. Subjects who received multiple doses of 10 mg, 20 mg, 40 mg or 60 mg of IONIS-ANGPTL3-LRx achieved dose-dependent, statistically significant mean reductions at day 37 in ANGPTL3 of up to 83 percent ($p \leq 0.001$). They also experienced statistically significant mean reductions in triglycerides of up to 66 percent ($p \leq 0.001$), in LDL-C of up to 35 percent ($p \leq 0.001$) and in total cholesterol of up to 36 percent ($p \leq 0.001$).

Amarin Corp. plc, of Dublin, reported data that further characterized the efficacy and safety of Vascepa (icosapent ethyl) in statin-treated women with persistent high triglyceride levels. The presentation of additional data from the ANCHOR study showed, consistent with overall study results, that prescription-pure EPA Vascepa reduced triglyceride levels and several other potentially atherogenic lipid parameters and inflammatory markers in a subgroup of statin-treated women with persistent high triglycerides. The post hoc analysis is published in the *American Journal of Cardiology*. Vascepa capsules are a single-molecule prescription product consisting of either 1 gram or 0.5 grams of the omega-3 acid commonly known as EPA in ethyl-ester form.

Amgen Inc., of Thousand Oaks, Calif., said that adding Repatha (evolocumab) to optimized statin therapy resulted in statistically significant regression of atherosclerosis in patients with coronary artery disease, according to data from the phase III GLAGOV coronary intravascular ultrasound imaging trial. GLAGOV evaluated whether the PCSK9 inhibitor would modify atherosclerotic plaque buildup in the coronary arteries of patients already treated with optimized statin therapy, as measured by intravascular ultrasound at baseline and week 78. Treatment with Repatha resulted in a statistically significant regression from baseline in percent atheroma volume (PAV), with those in the Repatha arm experiencing a 0.95 percent decrease vs. baseline in PAV compared with an increase of 0.05 percent vs. baseline in patients receiving optimized statin therapy plus placebo ($p<0.0001$). In addition, adding Repatha yielded plaque regression in PAV for a greater percentage of patients than for those receiving placebo (64.3 percent vs. 47.3 percent, respectively, $p<0.0001$).

Arrowhead Pharmaceuticals Inc., of Pasadena, Calif., reported preclinical data for its lipoprotein(a)-targeting candidate, ARC-LPA, and its factor XII-targeting candidate, ARC-F12, both of which the company said showed substantial improvements over previous RNAi-based generation triggers. Among the data presented included dose-dependent reductions in serum F12 levels observed with single injections of anticoagulant ARC-F12 of 1 mg/kg and 3 mg/kg, leading to mean reductions of 86 percent and 96 percent, respectively. In a rat arteriovenous shunt model, a statistically significant reduction ($p=0.002$) in thrombus weight was observed at greater than 95 percent F12 knockdown. Nonhuman primate studies of ARC-LPA showed a reduction of 85 percent to 90 percent of serum Lp(a) levels after three weekly 3-mg/kg SQ doses. In an atherosclerosis model, data suggest that RNAi triggers can be effectively delivered to a fatty liver using Arrowhead's DPCsq platform.

Boehringer Ingelheim GmbH, of Ingelheim, Germany, presented updated results from 494 patients in its ongoing phase III RE-VERSE AD study, showing that administration of 5 g of idarucizumab immediately reversed the anticoagulant effect of dabigatran, the active ingredient in Pradaxa (dabigatran etexilate mesylate). For group A patients with extracranial bleeding, median time to confirmation of hemostasis was 3.5 to 4.5 hours, depending on anatomical location. The source of bleeding was similar to the previous interim analysis. In group B, 93 percent of patients experienced normal hemostasis during surgery, and the median time to the operating room was 1.6 hours after administration of idarucizumab. Idarucizumab, marketed in the U.S. as Praxbind, gained approval as a specific reversal agent for the firm's oral anticoagulant. (See *BioWorld Today*, Oct. 9, 2015.)

CSL Behring, of King of Prussia, Pa., reported results from AEGIS-I, a phase IIb trial testing CSL112, an apolipoprotein A-I infusion therapy in development to reduce the high incidence of early recurrent cardiovascular events that occur in the weeks to months following a heart attack, most commonly due to additional rupture of vulnerable atherosclerotic plaque. AEGIS-I met its co-primary safety endpoints, showing that CSL112 does not cause significant changes in liver or kidney function and demonstrating that it is well-tolerated when administered in the acute myocardial infarction setting. The study also provided confirmation of CSL112's mechanism of action, cholesterol efflux enhancement, as demonstrated by an immediate, up to fourfold increase in cholesterol efflux capacity, compared to baseline. Results were published online in *Circulation*.

Cytokinetics Inc., of South San Francisco, reported additional results from its COSMIC-HF (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure) phase II trial evaluating omecamtiv mecarbil in patients with chronic heart failure and left ventricular systolic dysfunction. Results showed that omecamtiv mecarbil, an investigational cardiac myosin activator, improved left atrial (LA) structure and function in patients with chronic heart failure with reduced systolic function. Analysis showed that minimum and maximum left atrial volume (LAV) decreased over time, with a statistically significant reduction in minimum LAV at 20 weeks ($p=0.032$) in patients receiving omecamtiv mecarbil. Similarly, patients receiving omecamtiv mecarbil experienced statistically

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AMERICAN HEART ASSOCIATION 2016

significant improvements in LA emptying fraction at 12 and 20 weeks (p=0.018 and p=0.004, respectively). The drug is being developed with Thousand Oaks, Calif.-based **Amgen Inc.**

Novartis AG, of Basel, Switzerland, presented results of a new analysis demonstrating that Entresto (sacubitril/valsartan) tablets reduced the risk of all events – first and repeat heart failure (HF) hospitalizations as well as cardiovascular (CV) deaths that followed HF hospitalization – compared to enalapril among heart failure patients with reduced ejection fraction (HFrEF). The findings are from a post-hoc analysis of PARADIGM-HF, in which a total of 3,181 primary endpoint events (including 1,251 CV deaths) were observed during the median 27-month double-blind follow-up period. Using multiple statistical analysis models, investigators found that Entresto demonstrated a risk reduction of between 20 percent to 24 percent for all events (first-time and repeat events) compared to enalapril, findings that were consistent with the proven benefit of Entresto for reducing the risk of a first event in PARADIGM-HF (a 20 percent risk reduction compared to enalapril on the primary endpoint, a composite measure of time to CV death or first HF hospitalization).

Portola Pharmaceuticals Inc., of South San Francisco, reported results from three substudies of the pivotal phase III APEX Study of betrixaban, an oral, once-daily factor Xa inhibitor anticoagulant in development for the prevention of venous thromboembolism in acute medically ill patients. In a retrospective APEX substudy on stroke, researchers assessed the potential of extended-duration thromboprophylaxis with betrixaban compared with standard-dose enoxaparin to reduce the risk of stroke in hospitalized acute medically ill patients. Results found that extended-duration betrixaban significantly reduced all-cause stroke (0.54 percent for betrixaban vs. 0.97 percent for enoxaparin; RRR=44 percent) and ischemic stroke (0.48 percent for betrixaban vs. 0.91 percent for enoxaparin; RRR=47 percent) through 77 days of follow up. Findings were published in *Circulation*.

Viking Therapeutics Inc., of San Diego, reported data from its phase Ib trial of VK2809 in subjects with mild hypercholesterolemia, with an analysis of the study participants' atherogenic protein levels demonstrating that subjects experienced statistically significant reductions in lipoprotein(a), or Lp(a), and apolipoprotein B-100 (apo B). Following 14 days of VK2809 treatment, subjects experienced statistically significant placebo-adjusted, least square mean reductions in both Lp(a) and apo B across a range of doses. Reductions in apo B ranged from 20.2 percent at 5 mg ($p = 0.0008$) to 39.6 percent at 40 mg ($p < 0.0001$); reductions in Lp(a) ranged from 31.6 percent at 5 mg ($p = 0.12$) to 54.9 percent at 20 mg ($p = 0.002$). Comparable results were obtained with or without least square mean adjustments, which account for covariates in patient characteristics. VK2809 is an orally available small-molecule thyroid receptor agonist.

OTHER NEWS TO NOTE

OSE Immunotherapeutics SA, of Nantes, France, signed service agreements with **Selexis SA**, of Geneva, gaining access to research cell banks from the Selexis Suretechnology platform. The agreements are designed to help OSE advance two preclinical products based on immune activation and regulation: Effi-DEM is a new-generation checkpoint inhibitor that blocks the signals regulatory protein-alpha receptor expressed by myeloid suppressor cells and tumor-associated macrophages, and Effi-7 is a humanized monoclonal antibody targeting the CD127 receptor.

Pharmaxis Ltd., of Sydney, reported that the National Health and Medical Research Council has awarded it a research grant of A$421,545 (US$318,560) for development and testing of its Orbital Inhaler with a dry powder formulation of the antibiotic tobramycin for the treatment of cystic fibrosis. The company will work with the Sydney-based Woolcock Institute of Medical Research.

Sciclone Pharmaceuticals Inc., of Foster City, Calif., received an unsolicited, nonbinding proposal from a consortium led by GL Capital Management GP Ltd. and ABG Management Ltd. to acquire the company for $11.18 per share in cash. The proposal is subject to a number of contingencies, including financing, due diligence and documentation, it said.

IN THE CLINIC

Acadia Pharmaceuticals Inc., of San Diego, started ADVANCE, a phase II study to evaluate pimavanserin for adjunctive treatment in patients with negative symptoms of schizophrenia. Studies show that about 40 to 50 percent of schizophrenia patients suffer from prominent negative symptoms. There is currently no drug approved by the FDA for the symptoms. As a selective serotonin inverse agonist, pimavanserin is a new class of antipsychotic medication with a distinct mechanism of action targeting serotonergic 5-HT2A receptors while avoiding activity at dopamine and other receptors commonly targeted by other antipsychotics, the company said. ADVANCE is a 26-week, randomized, double-blind, placebo-controlled, multicenter study. About 380 patients will be randomized to receive either pimavanserin or placebo, orally, once daily, in addition to their ongoing antipsychotic in a flexible dosing regimen. The starting daily dose of 20 mg of pimavanserin at baseline may be adjusted to 34 mg or 10 mg during the first eight weeks of treatment. The primary endpoint of the study is the change from baseline to week 26 on the Negative Symptom Assessment-16 total score. Following participation in ADVANCE, patients will be eligible to enroll in a 52-week open-label extension study.

ACR 2016

The following data were presented at the American College of Rheumatology/Association of Rheumatology Health Professionals meeting in Washington.

Eli Lilly and Co., of Indianapolis, and **Incyte Corp.**, of Wilmington, Del., said that in two phase III trials, RA-BEAM and RA-BUILD, patients with rheumatoid arthritis treated with baricitinib experienced significant improvements in patient-reported outcomes, including joint pain, severity of morning joint stiffness and tiredness, compared to placebo and Humira (adalimumab, Abbvie Inc.). Baricitinib is a once-daily oral selective JAK1 and JAK2 inhibitor currently in late-stage studies for inflammatory and autoimmune diseases.

Morphosys AG, of Martinsried, Germany, said licensee Janssen Research & Development LLC, a unit of New Brunswick, N.J.-based **Johnson & Johnson**, presented results from a phase IIa study testing guselkumab, a fully human anti-IL-23 monoclonal antibody, in the treatment of active psoriatic arthritis. Data showed a substantially higher percentage of patients receiving guselkumab achieved at least a 20 percent improvement in signs and symptoms of the disease, or ACR20, at week 24, the study's primary endpoint, compared with patients receiving placebo. Results also showed statistically significant improvements in all secondary endpoints, including physical function, psoriatic skin lesions and other health-related outcomes in patients treated with guselkumab compared with patients receiving placebo.

Pfizer Inc., of New York, reported results from the phase III OPAL (Oral Psoriatic Arthritis Trial) studies, Broaden and Beyond, testing JAK inhibitor Xeljanz (tofacitinib citrate) in adult patients with active psoriatic arthritis who had an inadequate response (IR) to conventional synthetic disease-modifying antirheumatic drugs or to tumor necrosis factor inhibitors, respectively. Both studies met their primary efficacy endpoints showing a statistically significant improvement with tofacitinib 5 mg and 10 mg twice daily compared to treatment with placebo at three months as measured by ACR20 response (OPAL Broaden: $p \leq 0.05$ and $p < 0.0001$; OPAL Beyond: $p < 0.0001$, respectively), and change from baseline in Health Assessment Questionnaire Disability Index score (OPAL Broaden: $p \leq 0.05$ and $p < 0.001$; OPAL Beyond: $p < 0.0001$ and $p < 0.001$, respectively).

Samumed LLC, of San Diego, said a phase I trial testing its Wnt pathway modulator, SM04690, demonstrated potential for cartilage regeneration, as well as improvements in pain and function associated with osteoarthritis of the knee. In the modified intent-to-treat population at 24 weeks, subjects in the 0.07-mg cohort showed a statistically significant increase in mean medial joint space width (JSW) of 0.49 mm (SD ±0.75 mm, $p=0.02$) from baseline compared to placebo. Clinicians generally perceive an increase in joint space as evidence of potential preservation or regeneration of cartilage. From baseline to 24 weeks, no change in mean medial JSW was observed in the 0.03-mg cohort, a decrease in mean medial JSW of 0.15 mm was observed in the 0.23-mg cohort and a mean decrease of 0.33 mm was observed in the placebo cohort. A phase II study of SM04690 is ongoing. In a separate presentation, Samumed reported in vitro and in vivo results showing the potential of SM04690 in degenerative disc disease. SM04690 induced the proliferation and differentiation of nucleus pulposus (NP)-derived progenitor cells into chondrocyte-like NP cells, which are essential to the proper functioning of intervertebral discs, providing both structure and hydration. Phase I testing in that indication is expected to start next year.

UCB SA, of Brussels, Belgium, said *The Lancet* published full results from EXXELERATE, the first head-to-head superiority study of two treatments in the anti-TNF class, comparing Cimzia (certolizumab pegol) plus methotrexate (MTX) to Humira (adalimumab, Abbvie Inc.) plus MTX in adult patients with moderate to severe rheumatoid arthritis who were inadequate responders to MTX. The study did not meet its primary endpoints for superiority, demonstrating no statistically significant difference in efficacy between the two drugs in combination with MTX in both short-term (12-week) and long-term (two-year) evaluations. However, data from the study demonstrated that switching between those anti-TNFs without a washout period was beneficial to some patients.

IN THE CLINIC

Bayer AG, of Basel, Switzerland, disclosed a phase III study evaluating the efficacy and safety of a newly developed formulation of investigational medication nifurtimox (Lampit) in children of all age groups who have been diagnosed with Chagas disease. Nifurtimox is not approved by the FDA and there are no other FDA-approved treatments for children with Chagas disease, a potentially life-threatening illness caused by the protozoan parasite *Trypanosoma cruzi*. The pathogen is often transmitted by an infected mother to her newborn during pregnancy or childbirth. Nifurtimox is on the World Health Organization's (WHO) list of essential medicines for both adults and children, and WHO is distributing nifurtimox in its efforts to control Chagas disease by 2020. Since 2004, Bayer has given WHO a permanent supply guarantee for nifurtimox and provided financial assistance to support logistics and drug distribution.

Cellectar Biosciences Inc., of Madison, Wis., said it selected CRO INC Research to oversee its National Cancer Institute (NCI)-supported phase II trial testing CLR 131 in patients with multiple myeloma and select hematologic malignancies. The 80-patient study will include relapsed/refractory patients with multiple myeloma, chronic lymphocytic leukemia/small lymphocytic lymphoma, lymphoplasmacytic lymphoma, marginal zone lymphoma, mantle cell lymphoma and potentially diffuse large B-cell lymphoma, who have been treated with standard therapy for their underlying malignancies. It is set to start in the first quarter of next year. The company anticipates that its $2 million NCI grant will cover about 50 percent of the study's cost, and the terms of the grant allow Cellectar to pursue an additional $3 million for a pivotal phase III trial of the company's lead radiotherapeutic compound.

AASLD 2016

The following data were presented at American Association for the Study of Liver Disease meeting in Boston.

Arbutus Biopharma Corp., of Vancouver, British Columbia, presented preclinical results showing that capsid inhibitor AB-423 has a dual mode of action for treating hepatitis B virus (HBV), by inhibiting HBV DNA and cccDNA synthesis. Another presentation showed that second-generation RNAi agent ARB-1740 was shown to suppress multiple elements of HBV, including HBsAg, HBeAg, DNA, core antigen and all RNAs including the HBx transcript, as demonstrated in vivo. Arbutus also reported data from combination studies showing that AB-423 and ARB-1740 demonstrated synergistic activity against HBV rcDNA in vitro, as well as inhibition of HBV DNA and serum HBsAg in in vivo models. Triple combinations consisting of AB-423 plus ARB-1740 with direct-acting antiviral Baraclude (entecavir, Bristol-Myers Squibb Co.) or pegylated interferon provided the greatest reduction in serum HBV DNA.

Enanta Pharmaceuticals Inc., of Watertown, Mass., reported that 98 percent (n=102/104) of chronic hepatitis C virus (HCV)-infected patients with severe chronic kidney disease (CKD) achieved sustained virologic response following 12 weeks of treatment (SVR12) with partner North Chicago-based **Abbvie Inc.**'s investigational, pan-genotypic regimen of glecaprevir (ABT-493)/pibrentasvir (ABT-530) in the primary intent-to-treat (ITT) analysis. In a modified ITT analysis, SVR12 was achieved in 100 percent (n=102/102) of severe CKD patients. That analysis excludes patients who did not achieve SVR for reasons other than virologic failure. The data are from the phase III EXPEDITION-4 study, evaluating patients with chronic HCV infection across all major genotypes (GT1-6) and severe CKD.

Gilead Sciences Inc., of Foster City, Calif., presented results from an open-label phase II trial of ASK1 inhibitor selonsertib (formerly GS-4997) alone or in combination with the monoclonal antibody simtuzumab in patients with nonalcoholic steatohepatitis, or NASH, and moderate to severe liver fibrosis (fibrosis stages F2 or F3). The data demonstrate regression in fibrosis that was, in parallel, associated with reductions in other measures of liver injury in patients treated with selonsertib for 24 weeks. Patients receiving selonsertib demonstrated improvements in several measures of liver disease severity, including fibrosis stage, progression to cirrhosis, liver stiffness (measured by magnetic resonance elastography) and liver fat content (measured by MRI-proton density fat fraction).

Replicor Inc., of Montreal, presented preliminary interim analysis from its latest REP 401 trial testing HBsAg release inhibitor REP 2139 and a REP 2139 derivative with improved plasma and tissue clearance (REP 2165) in combination with Viread (tenofovir disoproxil fumarate, or TDF, Gilead Sciences Inc.) and pegylated interferon alpha-2a (peg-IFN) in treatment-naïve patients with chronic HBeAg-negative hepatitis B virus (HBV) infection. Control patients receiving peg-IFN + TDF exhibited minimal antiviral response beyond suppression of serum HBV DNA, while patients receiving REP 2139 or REP 2139 in addition to peg-IFN and TDF experienced robust, multilog reductions in HBsAg, increased levels of circulating anti-HBsAg antibodies and serum transaminase flares indicating restored immune response in the liver.

IN THE CLINIC

Clearside Biomedical Inc., of Alpharetta, Ga., enrolled the first patient in a phase I/II trial called HULK of Zuprata, its suspension formulation of the corticosteroid triamcinolone acetonide, for the treatment of diabetic macular edema. The HULK trial is an open-label, multicenter study designed to assess the safety and efficacy of the administration of Zuprata to the suprachoroidal space concomitant with intravitreal Eylea (aflibercept, Regeneron Pharmaceuticals Inc.), as well as suprachoroidal Zuprata monotherapy. The trial targets enrollment of about 20 patients, with about equal numbers in each of the two arms. Anatomical and functional data and safety information will be collected at each monthly visit during the six-month evaluation period.

Mallinckrodt plc, of Chesterfield, U.K., confirmed enrollment of the first patients in its phase IV study testing H.P. Acthar gel (repository corticotropin injection) in systemic lupus erythematosus (SLE) patients with persistently active disease. The randomized, double-blind, placebo-controlled trial is designed to build on data from a pilot study in patients with active SLE, recently published in *Lupus Science & Medicine*. H.P. Acthar gel is approved by the FDA for use during an exacerbation or as a maintenance therapy in select patients with SLE.

Modus Therapeutics AB, of Stockholm, a Karolinska Development AB company, said the independent data safety monitoring board, after a planned safety review, said adolescents, between the ages of 12 and 18, will now be enrolled in the ongoing phase II trial testing sevuparin for sickle cell disease (SCD). Modus said it also decided to increase the sample size of the study to about 150 patients. The trial is designed to demonstrate a reduced time to resolution of vaso-occlusive crises (VOC) in hospitalized SCD patients treated with sevuparin in comparison to those treated with placebo and is targeting a potential 30 percent reduction in the time to resolution of the VOC.

Nantkwest Inc., of Culver City, Calif., presented early analysis from its ongoing phase II Merkel cell carcinoma study at the Society for Immunotherapy of Cancer meeting in National Harbor, Md., showing that its activated natural killer, or aNK, cell therapy showed evidence of a radiological complete response following single-agent infusion in a patient with recurrent disease after multiple lines of therapy, including relapse after checkpoint inhibitor therapy.

IN THE CLINIC

Nivalis Therapeutics Inc., of Boulder, Colo., said it completed enrollment in the second of two phase II trials of cavosonstat (N91115), a stabilizer of the cystic fibrosis transmembrane conductance regulator (CFTR) protein, which is being evaluated as an add-on therapy to Kalydeco (ivacaftor, Vertex Pharmaceuticals Inc.) in adult patients who have one copy of the F508del mutation and a second mutation that results in a gating defect in the CFTR protein. A total of 19 patients have been enrolled in the U.S., and top-line results are expected in the first quarter of next year.

OWC Pharmaceutical Research Corp., of Petach Tikva, Israel, is submitting the final safety protocol for a planned early stage trial of its medical-grade cannabis cream to the Israeli national IRB committee at the office of the Health Minister. The 12-week trial will test multiple escalating doses of a topical creme infused with active cannabinoids to determine safety and tolerability in healthy volunteers.

Repros Therapeutics Inc., of The Woodlands, Texas, reported top-line results for both its pooled oral and vaginal delivery phase II studies in the treatment of uterine fibroids, both of which enrolled women with confirmed fibroids by MRI at baseline and who were experiencing more than 80 mL of blood loss during menses as confirmed by alkaline hematin assessment. Proellex at doses of both 6 mg and 12 mg, delivered by either route, substantially and significantly reduced excessive menstrual bleeding. Pooled oral and vaginal delivery vs. placebo met the primary endpoint of induction of amenorrhea ($p<0.0001$ and $p=0.0071$, respectively), and a statistically significant reduction in fibroid size from baseline was achieved by the combined active arms for the pooled oral dosage form compared to placebo ($p=0.0004$). The company said it will propose an oral route of administration for phase III development and plans to submit a request to the FDA before the end of this year to discuss the phase III program.

OTHER NEWS TO NOTE

Uni-Bio Science Group Ltd., of Hong Kong, established a strategic partnership with Shanghai-based **Luqa Pharmaceuticals Trading Co. Ltd.**, a China-focused specialty pharmaceutical company, to conduct co-promotion and co-marketing of dermatology drugs in mainland China, something Uni-Bio said would enable it to immediately expand its income stream and generate cash flow. Under the terms of the alliance, products for co-promotion and co-marketing cover drugs or medical devices for the treatment of dermatological disorders, including Uni-Bio Science's and Luqa's current and future products in the dermatology field. The three-year promotion agreement includes an option to renew for two additional years. While the agreement is in force, Uni-Bio Science will co-promote selected products in hospitals or qualified institutions, drug stores and retail channels in certain territories, it said. Uni-Bio Science will additionally support Luqa with market access in the territories, including provincial and national reimbursement expansion of products under collaboration. Financial details of the arrangements were not disclosed.

Uniqure NV, of Amsterdam, completed a companywide strategic review aimed at refocusing its pipeline, consolidating its manufacturing and enhancing overall execution. The company expects to realize €5 million to €6 million (US$5.4 million to $6.4 million) of annualized cost savings in personnel and other related operating expenses as a result of the elimination of approximately 50 to 60 positions, or 20 percent to 25 percent of its global headcount, by the end of 2017. Additionally, the company expects to further reduce planned operating expenses by €11 million to €15 million over the next two years through the focusing of its pipeline. Existing cash resources will be sufficient to fund operations into 2019, it said. The company will prioritize programs in hemophilia B, Huntington's disease and those associated with its collaboration with **Bristol-Myers Squibb Co.**, of New York, in cardiovascular disease. Additionally, the company will restructure its R&D organization in the Netherlands and consolidate manufacturing in the U.S. The actions are expected to reduce operating expenses and create a more efficient company focused on the development of gene therapies, it said.

Ziopharm Oncology Inc., of Boston, highlighted the publication of data demonstrating enhanced persistence of genetically modified T cells targeting leukemia through utilization of its nonviral Sleeping Beauty system to co-express membrane-bound IL-15 (mbIL15) and a CD19-specific chimeric antigen receptor (CAR). The article, "Tethered IL-15 augments antitumor activity and promotes a stem-cell memory subset in tumor-specific T cells," was published in the Nov. 14, 2016, issue of the *Proceedings of the National Academy of Sciences*.

REGULATORY FRONT

SEC Chair Mary Jo White announced that she will step down from the commission when President Barack Obama leaves office in January. White, who became chair of the SEC in April 2013, will be one of the longest serving chairs in the commission's history. During her time at the helm, the agency completed the majority of its mandates under the Dodd-Frank Act and all of its mandates under the JOBS Act. The commission also instituted a new approach to enforcement through enhanced data analytics and technology.

A **U.S. federal jury** in San Francisco found Sasan Sabdaran, the former director of drug safety risk management at Brisbane, Calif.-based Intermune Inc., and his friend Farhang Afsarpour liable for insider trading. The **SEC** charged the pair in October 2014, alleging that Sabdaran tipped Afsarpour with confidential details about Intermune's marketing application before the EMA for Esbriet (pirfenidone), a drug to treat idiopathic pulmonary fibrosis. Afsarpour, a restaurant owner in the U.K., traded on the tips by purchasing securities in his own accounts and on behalf of friends, generating more than $1 million in profits.

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