BIOWORLD™ TODAY

THE DAILY BIOPHARMACEUTICAL NEWS SOURCE

DECEMBER 2, 2014 BIOTECH'S MOST RESPECTED NEWS SOURCE FOR MORE THAN 20 YEARS VOLUME 25, NO. 232

CLINICAL TRIALS PART 2: GENDER

Who's the default? Increases in women's participation in studies bring uneven gains

By Anette Breindl, Science Editor

Twenty-four years after the NIH established the Office of Research on Women's Health, and 21 years after the NIH Revitalization Act of 1993 first required that women be included in clinical trials, certainly the letter of the law has been achieved. Women are now the majority of participants in NIH-funded trials.

The whole picture, though, is much more complex, and more uneven. Increased participation has led to gains in some areas. But in other areas, far too little is known about whether and how drug responses and optimal treatments differ for

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J&J options Modern's dual RANKL, TNF-alpha inhibitors in potential $277M deal

By Cormac Sheridan, Staff Writer

DUBLIN – Modern Biosciences plc (MBS) could earn up to £176 million (US$277 million) in up-front and milestone payments from an option and licensing deal with the Janssen Biotech Inc. arm of Johnson & Johnson that covers a series

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REPORT

ONLINE DATA GRAB

Big hack attack? Biotech target in capers by 'FIN4,' says security firm report

By Randy Osborne, Staff Writer

Half of the more than 100 firms targeted by a group of hackers out to intercept confidential data regarding potentially market-moving disclosures are biotech

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U.S. NEWS

SMALL MARKET, SAYS ANALYST

Avanir migraine CRL no investor surprise; hangup in device use

By Randy Osborne, Staff Writer

As expected, the FDA hit Avanir Pharmaceuticals Inc. late Wednesday with a complete response letter (CRL) related to the new drug application (NDA) for AVP-

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DEALS AND M&A

Astrazeneca partners with Cancer Research UK to find new targets

By Nuala Moran, Staff Writer

LONDON – Astrazeneca plc is extending its reach further into academic research in the UK, signing an agreement to give the medical charity Cancer Research UK (CRUK) access to its library of 2 million

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LATIN AMERICA

Abivax to commercialize Cuban vaccines from the Finlay Institute

By Sergio Held, Staff Writer

BOGOTA, Colombia – A deal between Cuban and French vaccine developers looks to tap into Cuba's strength as a vaccine producer while reaching out to markets in Asia and Latin America,

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NEWCO NEWS

Carsgen's China-led series A to fund clinical trials of CAR-T candidate

By Cornelia Zou, Staff Writer

HONG KONG – Carsgen, a Chinese developer of cancer therapies, announced its completion of an undisclosed series A financing led by China-based health care private equity

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FINANCINGS

Abeona Therapeutics Corp, of Cleveland, closed a $3.6 million financing to complete preclinical development of therapies to treat children with mucopolysaccharidosis type III, or MPS III, the rare genetic disorder also known as Sanfilippo syndrome. U.S. investors included Cure Sanfilippo Foundation, Sanfilippo Research Foundation, Team Sanfilippo, the Abby Grace Foundation and the National MPS Society. The round also included investments from Spain's Stop Sanfilippo and Sanfilippo B Foundation, Geneva-based Fondation Sanfilippo and Mexico's Red Sanfilippo Foundation. Sanfilippo syndrome, which has no approved treatments and no cure, is a group of four deadly genetic diseases that result from the body's inability to break down certain sugars properly. Abeona is focusing initially on gene therapies for Sanfilippo syndrome types A and B and expects to initiate human trials in early to mid-2015.

Alimera Sciences Inc., of Atlanta, inked an agreement with Deerfield Management and certain affiliates, which agreed to purchase approximately $50 million in Alimera preferred shares, contingent on undisclosed closing conditions. Alimera agreed to issue an additional 124.378 preferred shares as a subscription premium. The preferred stock may be converted into approximately 8.4 million common shares. Alimera plans to use the proceeds for U.S. commercial launch of its lead product, Iluvien (fluocinolone acetonide), continued marketing efforts in Europe and general corporate purposes. The financing is expected to close by Dec. 17. Iluvien was approved by the FDA in September to treat diabetic macular edema in patients previously treated with a course of corticosteroids who did not have a clinically significant rise in intraocular pressure. On Monday, Alimera's shares (NASDAQ:ALIM) slipped 27 cents to close at $5.60. (See *BioWorld Today*, Sept. 30, 2014.)

Ascendis Pharma A/S, of Copenhagen, completed a $60 million series D financing co-led by Sofinnova Ventures, Orbimed and Vivo Capital with participation from Janus Capital Management LLC, Venrock, RA Capital Management, Rock Springs Capital and Sectoral Asset Management. The company's largest existing shareholder, Sofinnova Partners, also participated. James Healy of Sofinnova Ventures, Jonathan Silverstein of Orbimed and Albert Cha of Vivo Capital joined Ascendis' board. The company said proceeds will be used to fund late-stage trials of Transcon growth hormone to treat growth hormone deficiency, or GHD, and in 2015 to initiate a phase I proof-of-concept program of Transcon treprostinil to treat pulmonary arterial hypertension. Proceeds also are expected to support drug manufacturing, advance the development of preclinical candidates and enhance the company's clinical development and research organizations.

Immune Pharmaceuticals Inc., of New York, said underwriters exercised in part their overallotment option of approximately 460,000 units at $2.50 apiece, bringing proceeds from the company's underwritten public offering to $9.685 million. The company issued approximately 3.9 million units, each consisting of one common share and one warrant to purchase 0.25 of a common share at an exercise price of $3.75 per share. Separately, $1 million invested recently by an existing investor was converted into 400,000 units consisting of 400,000 common shares and warrants to purchase up to 100,000 additional common shares. In total, the company raised $10.685 million in November. National Securities Corp. acted as sole book-running manager.

STOCK MOVERS 12/1/2014

Company	Stock in $	Change in %
Nasdaq Biotechnology	-$36.59	-1.15%
Calithera Biosciences	-$2.13	-19.96%
Glycomimetics Inc.	-$1.29	-13.33%
Pozen Inc.	-$1.26	-14.17%
Uniqure NV	-$1.78	-11.83%
Tekmira Pharmaceuticals	-$1.89	-10.83%

Biotechs showing significant stock changes Monday

BIOWORLD TODAY

BioWorld™ Today (ISSN# 1541-0595) is published every business day by Thomson Reuters, 115 Perimeter Center Place, Suite 1100, Atlanta, GA 30346 U.S.A.

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Gender

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men and women.

Not very long ago at all, the lack of women in clinical trials was due to outright discrimination. In 1977, the FDA barred women of childbearing age from participating in most early stage clinical research, a ban that was officially recognized as detrimental to women's health in the mid-1980s, when the NIH first adopted guidelines (that remained widely ignored until the NIH Revitalization Act of 1993) encouraging the inclusion of women in clinical research.

These days, the issue, as it often is with women's issues, is more complex.

It is clear that there has been progress. But it has been uneven, and perhaps surprisingly there is no obvious relationship between the success and whether a condition is specific to females or not.

Breast cancer, which is overwhelmingly a women's disease, was singled out in a 2010 Institute of Medicine report on women's health research as a condition where there has been much progress. Ovarian cancer, on the other hand – which can be due to the same underlying genetic factors in some cases – has seen little progress.

In diseases that can affect both men and women, progress has been equally mixed. The treatment of cardiovascular disease has made strides in women; treatment of lung cancer, not so much.

And even in trials in which women are equally represented, the data generated on their unique responses often go to waste.

Only a minority of trials analyze their subgroups separately – and so even if a treatment has different effects in men and women, those effects may not be recognized if such subgroup analysis is missing.

The Society for Women's Health Research (SWHR) is one organization that is pushing to make such subgroup reporting mandatory in practice. At an April FDA hearing on issues and challenges with the collection, analysis and availability of demographic subgroup data, SWHR president and CEO Phyllis Greenberger urged the FDA to "enforce existing regulations and guidance that require subgroup reporting and analysis be submitted by sponsors for the safety and effectiveness of all medical products. . . . The FDA should finalize draft guidance for sex-specific analysis they proposed in 2011 and issue similar guidance for race and ethnic minorities and the aged."

The SWHR has long lobbied for the inclusion of women – and minorities – in medical research as part of a broader focus on "transforming women's health through science, advocacy and education," according to the organization's mission statement.

Overall, the FDA and NIH "have improved a lot," Phyllis Greenberger told *BioWorld Today*. "If nothing else, they have improved in the recognition that it's important." And that improvement has been accelerating. "In 2014, we have probably made more progress than in the 24 years leading up to it."

But just how much progress has been made remains impossible to know.

For one thing, the NIH has "never broken down the trials by diseases," Greenberger pointed out. There is the real possibility that an overall participation rate of 50 percent may be the net result of a few large trials that are made up exclusively of women, plus many trials where women are still underrepresented.

Breast cancer, for example, is a very active trial area – much more active than its closest male-specific pendant, prostate cancer – and so breast cancer trials alone may contribute disproportionately to the overall number of women in trials.

With the passage of the 2012 FDA Safety and Innovation Act (FDASIA), Congress mandated that the FDA issue a public report on the extent to which demographic subgroups, including sex, age, race and ethnicity, are included in new drug applications.

In late November, as part of that effort toward greater transparency, the FDA released demographic "snapshots" of demographic information for the trials that led to the approval of six drugs in May and June of 2014. If they are snapshots, they are the equivalent of an embarrassing Instagram post.

While the majority of the trials did include separate analyses for men and women, patients older and younger than 65, respectively, were only analyzed separately in half of the trials.

And the analysis of racial subgroups was simply dismal. In only one of six trials – that for Jublia (efinaconazole, Dow Pharmaceuticals Inc.), approved in June 2014 for the treatment of onychomycosis, or toenail fungus – was minority participation sufficient to enable a separate analysis of different ethnic subgroups. That analysis found a trend toward greater efficacy in Asians, either because there was no difference or because the groups were too small – the data can't say. And according to the FDA snapshots website, "difference in side effects by race was not evaluated."

The data prompted the SWHR to issue a press release stating, "We commend the FDA for the effort in collecting and releasing these data to the public and we believe it is an initial first step towards reducing the disparities and lack of information on sex and ethnic differences. But as is evident, the percentage of minority participation is dismal and while there are women in all of the trials, the numbers are not statistically significant to reach any clinical relevance."

Not all trials are NIH-sponsored, either. Data from industry trials are largely confidential, but what data there are suggest that women are still underrepresented.

Industry, too, at least has an awareness of the problem. "Diversity in trial enrollment is something that we constantly worry about," Jesse Berlin, vice president of epidemiology at Johnson & Johnson, told *BioWorld Today*.

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Modern

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of preclinical bone-protective compounds in development for rheumatoid arthritis (RA) and potentially other indications. It would also gain royalties on eventual product sales.

Its lead drug candidate is entering the clinic next year, so it will be some time yet before J&J, of New Brunswick, N.J., will pull the trigger on the option. "We will run the phase Ia and phase Ib programs. Johnson & Johnson has the option to then license the program and take it in-house," Sam Williams, CEO of London-based MBS, told *BioWorld Today*.

Should it do so, some of the deal proceeds will flow north to Scotland, as MBS originally in-licensed the program from Osteorx Ltd., a University of Aberdeen spinout formed to commercialize the research of medicinal chemist Iain Greig, of the university's Kosterlitz Centre for Therapeutics, and collaborator Stuart Ralston of the University of Edinburgh.

They identified the compounds originally using a phenotypic screen – during early preclinical development, their mechanism was not understood. "We have a much better handle certainly on the mechanism of action," Williams said. "We haven't disclosed what the molecular target is."

What makes the compounds interesting is their dual role in inhibiting inflammation while protecting – and even promoting the growth of – bone, which undergoes erosion in RA.

That dual activity differentiates them from existing anti-inflammatory RA drugs, including tumor necrosis factor (TNF)-alpha inhibitors and Janus kinase (JAK) inhibitors, which exhibit bone protective effects indirectly. "They all act via damping down the inflammatory response. Our compounds have this direct impact on bone," he said. "The proof of that is the molecules work in models of osteoporosis, where there is no inflammation."

Greig and Ralston published preliminary work on the compound series in the Oct. 4, 2013, issue of *Annals of the Rheumatic Diseases*, in a paper, titled "Identification of small molecule inhibitors of RANKL and TNF signalling as anti-inflammatory and antiresorptive agents in mice."

According to the study, the compounds suppressed inflammatory arthritis, inhibited joint destruction and prevented systemic bone loss in the collagen-induced mouse arthritis model. One of them, ABD328, a biphenyl-carboxylate derivative, exhibited oral activity.

RANKL – the receptor activator of nuclear factor (NF) κB ligand – is the target of Thousand Oaks, Calif.-based Amgen Inc.'s fast-selling osteoporosis drug Prolia (denosumab). It is a key actor in bone tissue turnover, as it triggers the differentiation, activation and survival of osteoclasts, the cells that promote bone resorption. There is a certain amount of overlap between the two conditions, as RA patients are at an increased risk of developing osteoporosis.

How much of that risk is due to disease biology or to confounding factors, such as the use of glucocorticoids or the loss of mobility due to RA, remains an open question for now. But the MBS program, if it makes substantial progress in the clinic, could shed some light on that question.

The deal comes about two years after MBS received funding from the UK's Biomedical Catalyst scheme, which was conceived in order to help early stage companies or projects bridge the valley of death. The J&J deal means that MBS has done just that. //

FINANCINGS

Lexicon Pharmaceuticals Inc., of The Woodlands, Texas, completed concurrent financing transactions consisting of a public offering of approximately 49.8 million common shares, an $80 million convertible note offering and a private placement of approximately 149.3 million common shares to an affiliate of its largest shareholder, Invus LP. The offerings generated proceeds of approximately $280 million. The public stock offering remains subject to an overallotment option of up to 7.5 million additional shares, and the private convertible notes offering remains subject to an overallotment option of another $15 million in principal amount of the notes. Lexicon plans to use the proceeds to continue developing its drug candidates and for nonclinical research and development efforts. (See *BioWorld Today*, Nov. 24, 2014.)

Nanobiotix SA, of Paris, said it completed a private placement with Capital Ventures International, which includes purchase by the investor of 650,000 new shares for a total subscription amount of €10.4 million (US$13 million), representing about 4.85 percent of the company's outstanding shares prior to the placement. The price per share was set at €15.99, a 15 percent discount to the volume-weighted average price on the Euronext Paris exchange on each of the five trading days immediately preceding the issue date. Funds will help Nanobiotix in the development of NBTRXR3, its lead product in clinical testing for soft-tissue sarcoma. Shares of the company (PARIS:NANO) closed Monday at €17.56, down €0.24.

Neothetics Inc. (formerly Lithera Inc.), of San Diego, closed its initial public offering of 4.65 million common shares at $14 apiece, raising approximately $60.5 million. Piper Jaffray & Co. and Guggenheim Securities LLC were joint book-running managers, with Needham & Co. as co-manager. On Monday, the company's shares (NASDAQ:NEOT) lost 62 cents to close at $10.17.

Trevena Inc., of King of Prussia, Pa., said it intends to offer $40 million in common shares through an underwritten public offering. Barclays Capital Inc., Cowen and Co. LLC and Jefferies LLC were named as joint bookrunners, with JMP Securities LLC and Needham & Co. LLC as co-managers. In February, Trevena raised $66.64 million, including overallotments, in its initial public offering. On Monday, the company's shares (NASDAQ:TRVN) lost 50 cents to close at $4.72. (See *BioWorld Today*, Feb. 3, 2014.)

FireEye

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companies, according to a new report by the Milpitas, Calif.-based security firm FireEye.

Though only 14 pages long, the report – which dubs the culprits FIN4 collectively – made quite a media splash. "Hacking the Street? FIN4 Likely Playing the Market" is the title of the report, which said 13 percent of FIN4's targets are in the medical device sector, and more than two-thirds of the 100-plus publicly traded companies belong in the health care/pharmaceutical category. FIN4 seems most interested in those areas because stocks may move more dramatically in response to trial results and regulatory decisions, making insider trades more profitable.

Specifically, FIN4, operating since at least mid-2013, targets email accounts. First, the group identifies people involved in such transactions as mergers and acquisitions (M&A). Then, it sends "M&A-themed and SEC-themed lures with Visual Basic for Applications macros implemented to steal the usernames and passwords of these key individuals," said FireEye, which could not be reached for additional comment. FIN4 has developed fake Outlook pages, too, in order to capture targets' credentials. FIN4 "knows their targets," according to FireEye, and "themes appear to be written by native English speakers familiar with both investment terminology and the inner workings of public companies."

Many of FIN4's lures apparently are stolen documents from actual deal discussions that the group then "weaponized" with the macros and sent to individuals directly involved in the deal. "In some cases, the discussions were public knowledge and widely reported in the media, while others were still in the early exploration and due diligence phases," according to the report. "In one instance, we observed FIN4 simultaneously target five different organizations involved in a single acquisition discussion. The group targeted individuals at the five firms several months before the organizations' involvement in the acquisition talks went public."

FireEye's Mandiant Services, which provides "incident response" and security assessment, has "successfully driven threat actors out of the computer networks and endpoints of clients across every major industry," and was the first to provide evidence of a coordinated hacking campaign against U.S. biopharmaceutical firms by operatives in China. Typical attacks in that campaign took the form of malware that comes in through email attachments. Another approach is for hackers to infiltrate the networks of service providers and use them to attack target companies. Chinese hackers were said to have taken as much as 6.5 terabytes of information from a single company over a 10-month period, though the company was not disclosed. (See *BioWorld Today*, June 10, 2013.)

FIN4 has made itself "a fly on many walls," FireEye said in the report. "In several of our investigations, FIN4 targeted multiple parties involved in a business deal, including law firms, consultants and public companies," the report noted. "In one instance, FIN4 appeared to leverage its previously acquired access to email accounts at an advisory firm to collect data during a potential acquisition of one of the advisory firm's clients."

If the activities "are indeed part of a sustained effort to gain advance access to market-moving information, it would not be the first time that network intrusions have played a role in an insider trading case," FireEye conceded. But the scale and tactics set the group apart. "Our visibility into FIN4 is limited to their network operations, so we cannot say for certain what happens after they gain access to insider information. What we can say is that FIN4's network activities must reap enough benefit to make these operations worth supporting for over a year – and in fact, FIN4 continues to compromise new victims as we finish this report." //

OTHER NEWS TO NOTE

AB Science SA, of Paris, said it advanced a small-molecule SYK kinase inhibitor named AB8779 into full preclinical development. The compound, entirely owned by AB Science, was shown, in vitro, to have greater potency than tamatinib (R406), the active metabolite of anti-SYK inhibitor fostamatinib (Rigel Pharmaceuticals Inc.) but with an ultra-selective profile. Preclinical data demonstrated that AB8779 has biological activity in vitro and in vivo in inflammatory murine models of asthma and rheumatoid arthritis and suggested the candidate induces apoptosis of B-cell chronic lymphocytic leukemia cells and displays antitumoral activity in vivo in a mouse model of mantle cell lymphoma. AB8779 has shown no cardiotoxicity in vitro on both human and rat cardiomyocytes. In vitro safety pharmacology and pharmacokinetics studies showed that AB8779 has good bioavailability, with no mutagenic activity. (See *BioWorld Today*, July 24, 2013.)

Actinium Pharmaceuticals Inc., of New York, said the FDA granted orphan drug designation for Actimab-A, an alpha radiolabeled antibody in development for newly diagnosed acute myeloid leukemia (AML) in patients older than 60. The candidate is in a multicenter phase I/II trial. In November, the company reported positive interim data from the ongoing AML trial showing that median overall survival of seven secondary AML patients (with prior myelodysplastic syndrome, or MDS) in the study was 9.1 months, compared to historical norms of two months to five months, depending on treatment modality. Actinium expects to report additional data from the trial in 2015.

Avanir

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825, a drug-device combination product consisting of low-dose sumatriptan powder, delivered intranasally with a breath-powered delivery technology for the acute treatment of migraine.

Aliso Viejo, Calif.-based Avanir said in November that the agency had raised questions about the human factor validation study data in its preliminary written feedback to the company. The FDA's issues were provided via a Discipline Review letter, in which the agency requested that the company optimize the product-user interface and conduct additional human factor testing. Regulators also noted that the NDA review was not complete and that the agency could have more comments regarding the application.

In the CRL, the FDA echoed November's concerns, asking that Avanir "assess the root cause(s) of device use errors observed in the previously conducted human factors testing." Although a new human factors validation study will have to be done, the agency did not find any clinical or nonclinical safety or efficacy issues nor chemistry, manufacturing and controls issues, nor did regulators want any new clinical trials.

Jefferies analyst Thomas Wei noted in an earlier research report that drug-device combo products often hit snags and he anticipated the CRL. "Importantly, the FDA has not cited any clinical safety or efficacy issues regarding the product, and given sumatriptan is a well-known entity, we assume the review issues are related solely to the device aspect of the combo rather than the active ingredient," he wrote Nov. 10.

"Assuming the company receives a CRL on its PDUFA date later this month, we expect Avanir will need to run an additional human factor study, which are typically short in duration (a few weeks to a month)," Wei wrote, adding that the company can likely resubmit and get an FDA action date in the second half of next year. AVP-825, he pointed out, "is not a key driver of our investment thesis and we assume a small market opportunity."

Avanir's stock (NASDAQ:AVNR) closed Monday at $15, up 8 cents. //

IN THE CLINIC

Abivax, of Paris, said it successfully completed its phase I first-in-man study of ABX464, a small molecule with the potential to inhibit HIV replication. Through its mode of action, the compound was shown in preclinical testing in mice to induce a long-lasting HIV viral load reduction even after treatment had been stopped. The company plans to start a phase II study in patients with HIV.

Ampio Pharmaceuticals Inc., of Englewood, Colo., reported updates for the STRUT open-label portion of the multiple-injection study at week 20 of the study. In the seven-patient phase of 47-patient STRUT study, each patient received three 4-ml intra-articular injections, one at baseline, the second at two weeks and the third at four weeks. There were no drug-related serious adverse events reported during the first 20 weeks. In addition, the primary endpoint, the WOMAC A pain score, improved by 91.2 percent from baseline to 20 weeks.

PHARMA: OTHER NEWS TO NOTE

Abbvie Inc., of North Chicago, inked a licensing deal with the Medicines Patent pool for HIV meds lopinavir (LPV) and ritonavir (r), enabling other companies and organizations to reformulate and manufacture specially designed LPV/r and r pediatric treatments for distribution in low- and middle-income countries where 99 percent of children with HIV in the developing world live.

Baxter International Inc., of Deerfield, Ill., said it submitted a biologics license application to the FDA for the approval of BAX 855, an extended half-life recombinant factor VIII treatment for hemophilia A based on Advate [antihemophilic factor (recombinant)] and developed using pegylation technology from **Nektar Therapeutics Inc.**, of San Francisco.

CRUK

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compounds and to a new screening facility currently under construction in Cambridge.

Astrazeneca and CRUK scientists will work together on screening five targets per year arising from CRUK-funded research, with Astrazeneca having the first right to negotiate a commercial license to promising leads.

"We are very much aware the best novel targets are likely to reside in academe," said Steve Rees, vice president, screening sciences at Astrazeneca. However, he said, "when we in-license from academe we find we need to do significant work before we can move things into formal development."

In the CRUK collaboration, the company will be working with principal investigators who are leaders in their fields, providing them with access to high-quality chemistry and screening equipment not available in an academic setting. That will allow Astrazeneca to develop understanding of the targets and to build relationships with university scientists, leading to a "higher probability of success" for compounds that subsequently are in-licensed, Rees told *BioWorld Today*.

The CRUK agreement also is another sign of Astrazeneca's intent to create a "porous" open environment for innovation at its new global R&D center, currently under construction in Cambridge.

The company previously announced a collaboration with the UK's main bioscience funding agency, the Medical Research Council (MRC), to create a joint lead discovery facility at the new R&D labs.

Here, scientists employed by MRC will work alongside Astrazeneca scientists on 15 screens per year, against targets from all areas of disease biology, nominated by the MRC following traditional peer review.

In another collaboration announced in September, CRUK agreed to establish a joint laboratory in Cambridge with Astrazeneca's biologics arm Medimmune. As part of that agreement, scientists from both organizations will work side by side at the new CRUK-MEDI Alliance Laboratory.

Cancer Research UK is providing setup and operational funding for the biologics lab and will contribute a portfolio of novel drug targets together with a team of scientists. Medimmune will oversee the facility and provide access to its human phage display libraries and antibody engineering technologies.

In the case of the five CRUK small-molecule screens per annum to be run by Astrazeneca, the CRUK scientists will be seconded to the Cambridge lab on a temporary basis. Across the agreements with the MRC and CRUK, "we will gain through having academic scientists on site, creating a more innovative culture in Astrazeneca," Rees said.

The spur for closer collaboration on drug discovery is not only to get a first look at new targets, but also the recognition two or three years ago that Astrazeneca's 2 million-strong compound collection is an underused resource.

"We spent several hundred million dollars and a number of years putting it together, and we were only screening it ourselves," said Rees.

That prompted the company to run a small number of screens on behalf of academics at its site in Alderley Park, Cheshire, where the compound library resides currently. It also has established agreements with academic drug discovery groups in the U.S., Canada and Germany, in which Astrazeneca ships compounds for screening in the partners' facilities.

The agreements with MRC and CRUK will lead to a significant increase in the number of small-molecule screens Astrazeneca does for third parties. In 2014, the company will carry out 10 external screens.

On the basis of deals signed to date, that will double in 2015. As the Cambridge center comes on line in 2016 – 17, the number will double again to 40.

"This is huge opportunity for academics and for Astrazeneca. Hopefully, projects will move into our pipeline," Rees said. Of 20 screens per annum it is planned to run against MRC and CRUK-nominated targets, "if we in-license two [compounds] as a result, that would be a fantastic return."

MRC and CRUK were early to recognize the need to fill the gap between the typical outputs of grant-funded research and programs suitable for in-licensing by pharma, and have set up their own drug screening operations. However, they acknowledge these cannot match the high-quality chemistry and the screening capabilities of a big pharma company.

The two also see this as an opportunity for their scientists to access training and gain expertise in drug discovery, a skill that is scarce in academe. //

OTHER NEWS TO NOTE

Aeterna Zentaris Inc., of Quebec City, and **Sinopharm A-Think Pharmaceuticals Co. Ltd.,** of Changchun City, China, signed an exclusive license and technology transfer agreement covering the Chinese, Hong Kong and Macau markets for Aeterna's lead cancer compound, zoptarelin doxorubicin, for the initial indication of endometrial cancer. The synthetic peptide carrier linked to doxorubicin is in a phase III ZoptEC (Zoptarelin doxorubicin in Endometrial Cancer) trial. Aeterna Zentaris will be entitled to a nonrefundable $1 million technology transfer fee, and Sinopharm A-Think agreed to additional undisclosed payments on the achievement of pre-established regulatory and commercial milestones. Aeterna Zentaris also is set to receive royalties on sales of zoptarelin doxorubicin in the licensed territory. Sinopharm A-Think will be responsible for the development, production, registration and commercialization of the compound in the territory. On Monday, Aeterna's shares (NASDAQ:AEZS) gained 12 cents, or 23 percent, to close at 64 cents.

Abivax

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The Finlay Institute, of Havana, has signed an agreement with Abivax SAS, of Paris, that will allow the Cuban institute to reach Asian and Latin American markets with three types of vaccines.

The agreement gives Abivax exclusive and nonexclusive distribution rights for the vax-TyVi vaccine against typhoid, the Va-Mengoc-Bc vaccine against Meningococcus groups B and C and vax-Spiral, which targets leptospirosis.

"Cuba is very established as a vaccine manufacturer, [with its] standards according to the World Health Organization, low costs of goods [and] large scale capacity, so there are a number of advantages that we will gain with this collaboration with Cuba," Hartmut Ehrlich, CEO of Abivax, told *BioWorld Today*.

The agreement grants distribution rights to Abivax in markets like India, Indonesia and the Philippines in Asia, and Mexico, Argentina, Brazil and Uruguay in Latin America.

"The Finlay Institute will be responsible for the cost-competitive production of all three vaccines," said Abivax.

Abivax will take advantage of its commercial network in both regions, while partnering with local distributors in each of the markets.

"Abivax will select its partners based on a number of criteria, including ability to service the selected market, portfolio fit and strength of relations with the local authorities," said the company.

The French company along with its local partners will be responsible for fulfilling all regulatory requirements in each market in Latin America and Asia. Abivax and the Finlay Institute expect to start selling the vaccines from this agreement in 2015. "We will be able to significantly support these markets selling the vaccine. [We are planning to] hit the markets right away," Ehrlich said.

The agreement establishes both exclusive and nonexclusive rights of distribution in the different territories that it comprises. Exclusive rights are granted for markets in which the vaccines have not entered yet. "There are some very large markets where the vaccines are not yet licensed," said Ehrlich. "In the next couple of months [the plan is to] work with the local licensing authorities, for example for the typhoid vaccine in India and Indonesia, to find the criteria that these countries have [for the vaccines to enter these markets]," he added.

The company is still assessing the potential of those markets in terms of sales. Nonexclusive rights are granted for markets in which the Finlay Institute is already in through government-to-government partnerships negotiated by the Cuban government.

"We believe that the markets that are already served by the Finlay Institute are not really exploited to the maximum," Ehrlich said.

For Ehrlich, the agreement with the Cuban center represents a very interesting opportunity. "It is a substantial opportunity and it is twofold: to build the market and, over the years, to develop these contracts to very lucrative markets," he said.

The company has focused on building a strong relationship with the government of the Island.

"All this is based on the relation that Abivax has been building with the Cuban government and the Cuban vaccine centers," said Ehrlich. "Abivax is ahead of the big pharma in terms for partnerships with Cuba; we are really ahead of the curve," he added

And beyond the three vaccines of that agreement, the French company aims to take advantage of this new commercialization network to also introduce ABX 203, a therapeutic vaccine candidate to treat chronic hepatitis B.

ABX 203 was licensed early this year to Abivax by the Cuban Center for Genetic Engineering and Biotechnology in Havana. The vaccine is currently under development.

"The trials have been going very well. It was initially developed in Cuba until phase II," said Ehrlich. "We are now implementing a final phase III clinical study in [Africa] that actually is going very well. We are anticipating to have the first patient treated in this phase III study before the year is over," he added.

The company is also developing ABX 464, a small molecule against HIV. The intellectual property rights of that molecule belong to Abivax.

The vaccines' agreement is only a first step in strengthening the relationship between Abivax and Cuba. "We are in further negotiations with some of the compounds under development," said Ehrlich, who did not provide any details on the negotiations. //

OTHER NEWS TO NOTE

Affymax Inc., of Cupertino, Calif., said its board adopted a tax benefit preservation plan to preserve the value of its net operating loss carryforwards (NOL) in relation to potential limitations under section 382 of the Internal Revenue Code. The company had federal NOLs of approximately $481 million as of Dec. 31, 2013. A substantial portion of those are limited due to a prior ownership change defined in the Code, and the company said its use of the remaining NOLs could be further limited under another ownership change, including a cumulative change in ownership by 5 percent shareholders, as defined in the code. The company said the rights plan was designed to serve the interests of stockholders by helping to protect its ability to use its NOLs to offset future tax liabilities. In connection with adoption of the rights plan, the company's board declared a nontaxable dividend of one preferred share purchase right for each outstanding common share to shareholders of record as of Dec. 8. While the rights plan is in effect, any individual or group that acquires beneficial ownership of 4.99 percent or more of the company's common shares without board approval would be subject to significant dilution in their ownership interest. Shareholders who currently own 4.99 percent or more of common shares will not trigger the rights unless they acquire additional shares.

Carsgen

Continued from page 1

fund BVCF Management Ltd. The proceeds will be used to initiate the clinical trials of Carsgen's lead therapeutic asset.

The biotech company focuses on the development of chimeric antigen receptors T-cell (CAR-T) immunotherapy to treat various cancers such as liver, lung, stomach and brain cancers.

"Carsgen is the first company to start a clinical study in human liver cancer with its proprietary technology platform," said Rachel Zhao, principal at Shanghai-based BVCF. While CAR-T cell treatment is accepted as the most potential cell immunotherapy, testing has focused more on hematologic rather than solid tumor targets.

"With our investment, the company would be able to build its cell treatment lab and start to recruit patients for its first pilot trial in liver cancer; the latter part would be the main purpose of the proceeds," Zhao added.

Carsgen will collaborate on the clinical trial with the Shanghai Cancer Institute and Shanghai Renji Hospital, with whom it has cooperated before. The company plans to initiate clinical studies with the fund for its lead therapeutic, KJgpc3-001, a glypican-3 (GPC3)-directed CAR-T cell therapy for liver cancer. KJgpc3-001 takes T cells extracted from the patient, genetically modifies them to express a chimeric antigen receptor for glypican-3 and then returns them to the body to attack the cancer cells. GPC3 is often overexpressed in liver cancers, or hepatocellular carcinoma (HCC). Preclinical studies have shown that KJgpc3-001 is able to kill HCC cells.

"HCC is the fifth most common cancer and the third most common cause of cancer mortality worldwide," said Li Zonghai, CEO of Carsgen. "The vast majority of liver cancer patients live in China and, unfortunately, it remains underdiagnosed and inadequately treated, with a very high rate of death within the first five years of diagnosis. Carsgen's game-changing CAR-T approach offers new hope for HCC patients."

The World Health Organization reported 745,000 cases of liver cancer cases around the world in 2012. Liver resection surgery is by far the most effective treatment for HCC, but tumor recurrence is very high. And the five-year survival rate is only 10 percent. However, most HCC patients are diagnosed at late stage, so potentially curative therapies, including chemotherapy, are often ineffective. The medical need for new therapies to treat the prevalent disease remains unmet.

"The leadership team [of Carsgen] has a strong background in cancer biology, cancer immunology and antibody development, as well as clinic cellular therapy technology and has assembled a strong proprietary position in CAR-T cell therapy specifically," said Yang Zhi, founder and managing partner of BVCF. "Additionally, Carsgen has established a great working relationship with several prominent hospitals in Shanghai, including Renji Hospital, the first Western medicine hospital in Shanghai."

While Carsgen is planning its initial clinical trials for KJgpc3-001, it is advancing its CAR-T therapies for lung and brain cancers at the same time.

Further details of the investment were not disclosed. But "the company plans to raise another round with milestones in the trial," said Zhao.

"We only invest in companies that are at the early growth stage – not start-up companies but companies that have been there a little while," Yang told *BioWorld Today* in a previous interview. "What I value in health care companies are teams, products that differentiate them from others and relatively mature technologies."

BVCF has invested in close to 20 biotech or health care companies such as Sinobiopharma Inc., Nod Pharmaceuticals Inc. and Allgens Co. and already has exited from investments into some large domestic biotech companies such as Citic Pharmaceuticals Co. and vaccine maker Ealong Biotech, which was acquired by Simcere Pharmaceutical Co. Ltd. in 2009.

The sponsors of BVCF are mainly strategic investors, which include pharmaceutical companies, institutional investors and foundations.

In April, BVCF, previously known as Bioveda, secured its third fund, BVCF III Fund LP, to invest $188 million in pharmaceuticals, medical technology, health care services and biotech companies in China. (See *BioWorld Today*, April 18, 2014.)

Besides Carsgen, some of the other investments of BVCF's newly completed BVCF III Fund include companies such as gene tech company Beijing Biocytogen Co. and U.S. company Micurx Pharmaceuticals Inc., which focuses on antibiotics.

The previous dollar-fund BVCF raised, Bioveda China Fund II, closed at $90 million in 2008. BVCF also has an RMB-denominated fund of ¥300 million (US$48 million) and is planning a second and larger one. //

OTHER NEWS TO NOTE

Alimera Sciences Inc., of Atlanta, said Iluvien, its sustained-release intravitreal implant designed to deliver fluocinolone acetonide, was granted marketing approval in the Netherlands for the treatment of vision impairment associated with chronic diabetic macular edema considered insufficiently responsive to available therapies.

The FDA issued a safety communication warning that a patient with multiple sclerosis who was treated with Tecfidera (dimethyl fumarate) from Cambridge, Mass.-based **Biogen Idec Inc.** for more than four years developed the rare and serious brain infection progressive multifocal leukoencephalopathy, or PML, and later died. Prior to developing PML, the patient had a very low number of lymphocytes in her blood. The agency said information describing the case was being added to the Tecfidera drug label. The patient was not taking other drugs that affect the immune system or drugs thought to be associated with PML, which is caused by the John Cunningham virus. The agency said the case was the only confirmed incidence of PML reported in patients taking Tecfidera. Biogen initially reported the PML case in its third quarter earnings. (See *BioWorld Today*, Oct. 23, 2014.)

Gender

Continued from page 3

CONFLICTING GOALS INTERFERE

But goals within trials can conflict. A biopharma company's first goal is to show that its experimental drug is safe and effective – without breaking the bank with its trials.

That goal begins with the need to get trials enrolled, so they do not drag on. If a trial is enrolling based on who shows up, and a condition is more prevalent in one sex, the other sex will end up underrepresented by default.

More generally, Berlin said, signal is easiest to distinguish from noise when trial populations are homogenous. Adding heterogeneity of trial participants means "you're adding heterogeneity of response."

For that reason, one line of reasoning holds that trials should pay particular attention to subgroup analyses only when there are a priori reasons to suspect that there will be biological differences. In a 2009 paper on the inclusion of women in clinical trials, Berlin and his colleague Susan Ellenberg wrote that "there is no question that some treatments do work differently in men and women, but the proportion of treatments for which men and women respond very differently is unknown."

The reason it is unknown leads smack into the next problem: Preclinical research, too, has long focused on male animals, and so in many cases there might be a priori reasons to suspect sex differences in reactions – if anyone were looking for them.

The NIH has been addressing the issue of sex bias in preclinical research. Earlier this year, the NIH announced it was developing policies that require applicants to balance sex of animals, and cell lines, in future grant applications, "unless sex-specific inclusion is unwarranted, based on rigorously defined exceptions."

In September, the agency awarded more than $10 million in supplemental grants to enable grantees to study the effects of sex in preclinical and clinical research.

At a meeting of the NIH's Office of Research on Women's Health, NIH director Francis Collins said that "we don't want to rush into this in a way that seems heavy-handed or clumsy. But we are dead serious about actually implementing change in a way that is going to address an issue that has been neglected."

More generally, the notion that one sex is data and the other, somehow, noise, is itself a consequence of considering male physiology the norm.

As Greenberger said, if the point is to reduce noise, "why don't we do all research on women and see what happens to men in phase IV?"

Considering men the norm from which women deviate also means that clinical trials are designed in a way that can make participation hard for women. For example, more frequent office visits and overnight stays required by trial design can make women, who are more often caregivers, less likely to enroll in trials.

And efforts of the NIH and FDA have been concentrated in late-stage trials, while the sort of safety data that could result from differences in metabolism are the provenance of early stage trials.

PREGNANT WOMEN: AN ORPHAN POPULATION

Nowhere are those issues starker than in the subgroup of pregnant women, who remain, in the words of Maggie Little, "an orphan population" with respect to drug development.

This despite the fact that conditions such as diabetes and hypertension and neuropsychiatric illnesses – primarily depression – affect hundreds of thousands of pregnant women annually.

Little is a co-founder of the Second Wave Initiative, which advocates for a greater inclusion of pregnant women in clinical trials through a mix of incentives, changes in regulations and innovative trial designs.

Pregnant women, she told *BioWorld Today*, "are an ethically complex population. . . . Everyone agrees we have to limit the risk to the fetus, because it can't consent."

But rather than excluding pregnant women from research, the solution needs to be to design protocols "that pass ethical muster and still get us the data we need."

If women are sometimes implicitly considered extraneous, pregnant women can find themselves considered – implicitly or even explicitly – as little more than cargo vessels for the duration of their pregnancy.

In a case statement, on their website, the Second Wave Initiative points out that "seriously ill pregnant women who might medically benefit from participating in research can be denied access without any justification or review – a standard not applied to any other population."

Yet the consequences of not taking drugs during pregnancy can be worse than the consequences of taking them, for mother and fetus alike. This is well documented for maternal asthma, which is associated with worse outcomes for babies if it is poorly controlled during pregnancy, but not if it is well controlled – with drugs.

The bottom line, Little said, is that "pregnant women get ill, and ill women get pregnant. . . . It's research we need to figure out how to do."

Editor's note: BioWorld's Clinical Trial series continues in Wednesday's issue, with a focus on race and ethnicity. //

PHARMA: OTHER NEWS TO NOTE

Boehringer Ingelheim GmbH, of Ingelheim, Germany, said the European Commission granted marketing approval for Vargatef (nintedanib), valid for the 28 countries within the European Union, for use in combination with docetaxel in adults with locally advanced, metastatic or locally recurrent non-small-cell lung cancer of adenocarcinoma tumor histology, after first-line chemotherapy. Nintedanib is a triple angiokinase inhibitor.

OTHER NEWS TO NOTE

Can-Fite Biopharma Ltd., of Petach Tikva, Israel, reported the publication of findings by researchers at St. Louis University and the NIH on the use of lead compound CF101, generically known as IB-MECA, to prevent neuropathic pain. According to the research, the compound bound with high affinity to the A3 adenosine receptor and reduced neuropathic pain through specific mechanistic pathways in animal models. Can-Fite holds an exclusive worldwide license from the NIH for clinical development of IB-MECA and the related compound, Cl-IB-MECA (CF102).

Clementia Pharmaceuticals Inc., of Montreal, said the FDA granted fast track designation to palovarotene, which is in development to treat fibrodysplasia ossificans progressive, or FOP, a rare, disabling genetic disease characterized by painful, recurrent episodes of soft tissue swelling and abnormal bone formation. The process, known as heterotopic ossification, occurs in muscles, tendons and ligaments, causing morbidities and progressive disability. Palovarotene, a retinoic acid receptor gamma agonist, is in phase II development.

Dynavax Technologies Corp., of Berkeley, Calif., regained full rights to DV1179, its investigational bifunctional inhibitor of Toll-like receptors (TLR) 7 and 9, following expiration of a potential $810 million research and development collaboration and license agreement with **Glaxosmithkline plc** (GSK), of London, that was executed in 2008. Under the collaboration, Dynavax conducted a phase I study of DV1179 to assess safety and tolerability and a phase Ib/IIa study of safety and pharmacodynamics in patients with active systemic lupus erythematosus (SLE). In the SLE study, doses up to 60 mg/week for eight weeks were well tolerated but DV1179 did not meet pharmacodynamic endpoints related to reduction in interferon alpha-regulated genes and GSK declined to exercise its license option. Dynavax now holds global rights to continue the development of DV1179 and other TLR 7/9 inhibitors for all indications, and the company said nonclinical data suggest DV1179 may have utility in a range of other indications, including treatment of conditions such as autoimmune pancreatitis and nonalcoholic steatohepatitis. Dynavax also is assessing the potential of DV1179 in autoimmune diseases with localized rather than diffuse systemic manifestations, such as scleroderma and dermatomyositis. On Monday, the company's shares (NASDAQ:DVAX) fell 77 cents to close at $14.09. (See *BioWorld Today*, Dec. 18, 2008.)

Editas Medicine, of Cambridge, Mass., signed genome-editing agreements with three academic institutions. The company inked an exclusive joint license agreement with the Broad Institute of the Massachusetts Institute of Technology and Harvard and Harvard University to access intellectual property and technology related to its CRISPR/Cas9 and TALE genome-editing systems. Separately, Editas signed exclusive license agreements with Duke University and with Massachusetts General Hospital to access intellectual property and technology related to the CRISPR/Cas9 and TALEN genome-editing systems. (See *BioWorld Today*, Nov. 25, 2013.)

Gilead Sciences Inc., of Foster City, Calif., licensed nonexclusive rights to Mylan Inc. subsidiary **Mylan Laboratories Ltd.**, of Hyderabad, India, to manufacture and distribute Gilead's investigational antiretroviral drug tenofovir alafenamide, a therapy for HIV-1, as both a single-agent product and in combination with other drugs. The license extends to 112 countries, which together account for more than 30 million people living with HIV, representing 84 percent of those infected globally. Terms of the deal were not disclosed.

Hanall Biopharma Co. Ltd., of Seoul, South Korea, and **Open Monoclonal Technology Inc.**, of Palo Alto, Calif., said they formed an alliance providing Hanall with a license to use OMT's Omnirat, Omnimouse and Omniflic platform for the generation of human antibodies against the neonatal Fc receptor and other undisclosed target antigens. Financial terms were not disclosed.

Immunocellular Therapeutics Ltd., of Los Angeles, said the EMA provided scientific advice supporting the advance of ICT-107 to a registrational phase III program in patients with newly diagnosed glioblastoma, consistent with positive feedback the company received from the FDA in relation to the scope, design and endpoints of a pivotal program and the inclusion of patients based on human leukocyte antigen, or HLA, and O-6-methylguanine-DNA methyltransferase, or MGMT, gene status. Immunocellular plans to design the phase III program with the goal of ensuring harmony between U.S. and EU trial protocols and seek to initiate the studies in 2015. (See *BioWorld Today*, Dec. 13, 2013.)

Intelgenx Corp., of Saint Laurent, Quebec, and **Redhill Biopharma Ltd.**, of Tel Aviv, Israel, said the German Federal Institute for Drugs and Medical Devices validated the marketing authorization application (MAA) for Rizaport, an oral thin film formulation of rizatriptan for acute migraines, and initiated the formal review process, with feedback on the MAA expected during the second half of 2015.

Jade Therapeutics Inc., of Salt Lake City, was awarded a two-year, $725,000 phase II Small Business Innovation Research grant from the National Science Foundation for its biodegradable polymer film for sustained delivery of antibiotics to the surface of the eye. The company is addressing the treatment of bacterial keratitis (BK)/corneal ulcers. Bacteria such as *Staphylococcus aureus* and *Pseudomonas aeruginosa* often lead to BK, precipitating medical attention to prevent corneal perforation.

Karyopharm Therapeutics Inc., of Newton, Mass., said its lead candidate, Selinexor (KPT-330), received orphan drug designation from the EMA to treat chronic lymphocytic leukemia and small lymphocytic lymphoma, including Richter's transformation, and to treat multiple myeloma. The drug previously received orphan designation in acute myeloid leukemia and diffuse large B-cell lymphoma from both the EMA and the FDA. (See *BioWorld Today*, Nov. 7, 2014.)

OTHER NEWS TO NOTE

Momenta Pharmaceuticals Inc., of Cambridge, Mass., said the FDA granted fast track designation to necuparanib, its oncology drug candidate, as first-line treatment in combination with Abraxane (nab-paclitaxel, Celgene Corp.) and gemcitabine in metastatic pancreatic cancer. Momenta recently completed part A of a phase I/II study and initiated proof-of-concept part B.

Nordic Nanovector ASA, of Oslo, Norway, and **Affibody AB**, of Solna, Sweden, signed a three-year collaborative research agreement to discover and develop advanced radioimmunotherapies (RITs) for multiple myeloma. Backed by a Eurostars grant, the project will combine Affibody's platforms with Nordic Nanovector's radioimmunotherapy technology. The project aims to provide documentation necessary to start GMP manufacturing of the Affibody-based RIT and subsequently to start clinical trials. Upon successful conclusion of the collaboration, Nordic Nanovector will have the opportunity to license the global rights to the Affibody-based RIT. The companies were awarded approximately €1 million (US$1.25 million) by Vinnova in Sweden and The Norwegian Research Council. (See *BioWorld Today*, July 1, 2014.)

Pharmacyclics Inc., of Sunnyvale, Calif., said the EMA accepted a type II variation application for Imbruvica (ibrutinib), filed by partner Janssen-Cilag International NV, a unit of New Brunswick, N.J.-based **Johnson & Johnso**n, as a potential label expansion for the drug in the European Union to treat adult patients with Waldenstrom's macroglobulinemia (WM). If approved, Imbruvica would be the first label specifically authorized to treat the rare B-cell lymphoma. Acceptance of the WM type II variation submission for Imbruvica triggered a $20 million milestone payment to Pharmacyclics under its collaboration agreement with Janssen Biotech Inc. (See *BioWorld Today*, Nov. 14, 2013.)

Pieris AG, of Freising, Germany, achieved a second milestone payment in its second Anticalin-targeted protein drug discovery and development collaboration with **Daiichi Sankyo Co. Ltd**., of Tokyo, triggering an undisclosed payment. The milestone is part of a partnership that could yield up to €100 million (US$124.7 million) per program for Pieris. The German company will now transfer development responsibility of the program to Daiichi, which will initiate further in vivo studies in nonhuman primates. (See *BioWorld Today*, April 13, 2011.)

Pozen Inc., of Chapel Hill, N.C., saw shares (NASDAQ:POZN) fall 14.2 percent, to close at $7.63 Monday, as Sanofi US, a unit of Paris-based **Sanofi SA,** returned all rights to the gastrointestinal-friendly aspirin candidates PA8140 and PA32540. The termination follows an FDA complete response letter that raised third-party manufacturing issues in April. Pozen said it will evaluate all strategic options for the drugs ahead of their Dec. 30 PDUFA date. Meanwhile, the enteric-coated aspirin/omeprazole combo candidates got a name: Yosprala 81/40 for the pill containing 81 mg of aspirin and Yosprala 325/40 for the pill with 325 mg of aspirin. (See *BioWorld Today*, April 29, 2014.)

Regeneron Pharmaceuticals Inc., of Tarrytown, N.Y., said Eylea (aflibercept) gained FDA breakthrough therapy status for the treatment of diabetic retinopathy in patients with diabetic macular edema (DME). The designation is based on positive results in two phase III trials, VIVID-DME and VISTA-DME, in which Eylea demonstrated a statistically significant improvement in a pre-specified measure of diabetic retinopathy in patients with DME after two years of treatment. There are no FDA-approved medicines for diabetic retinopathy. Eylea is already approved in the U.S., European Union and other countries for the treatment of wet age-related macular degeneration, macular edema following central retinal vein occlusion and DME. In separate news, partner **Bayer AG**, of Leverkusen, Germany, said it received approval from Health Canada for Eylea for the treatment of DME.

Treeway BV, of Rotterdam, the Netherlands, said the EMA granted orphan status for TW001, its lead candidate for the treatment of amyotrophic lateral sclerosis (ALS). In October, the company inked an agreement with the Leiden Academic Center for Drug Research to collaborate in optimizing trial designs and data analysis for ALS, with the goal of developing a population disease progression model that may be used for a phase III study. (See *BioWorld Today*, Oct. 20, 2014.)

IN THE CLINIC

Exelixis Inc., of South San Francisco, reported top-line results from the final analysis of COMET-2, its randomized, double-blind, controlled trial of cabozantinib in men with metastatic castration-resistant prostate cancer (mCRPC) who are suffering from moderate to severe pain despite optimized narcotic medication, and whose disease has progressed following treatment with docetaxel as well as Zytiga (abiraterone, Johnson & Johnson) and/or Xtandi (enzalutamide, Medivation Inc. and Astellas Pharma Inc.). Fifteen percent of patients in the cabozantinib arm reported a pain response, compared to 17 percent of patients in the control arm receiving mitoxantrone/prednisone, a difference that was not statistically significant. The safety profile of cabozantinib in the trial was consistent with that observed in previous studies in mCRPC. Exelixis de-prioritized cabozantinib in mCRPC in September, following disappointing data from the COMET-1 study. The company also, at that time, initiated a work force reduction to focus development efforts and resources on the pivotal phase III studies of cabozantinib in metastatic renal cell carcinoma and advanced hepatocellular carcinoma. Shares of Exelixis (NASDAQ:EXEL) fell 17 cents, or 10.2 percent, to close Monday at $1.49. (See *BioWorld Today*, Sept. 3, 2014.)

Galmed Pharmaceuticals Ltd., of Tel Aviv, Israel, said it completed the statistical analysis of a pharmacokinetic study of three doses, including two high doses (400 mg and 600 mg), of its drug candidate, aramchol, in 66 healthy adult male volunteers. No serious adverse events were observed. Results support the firm's decision to administer the two higher doses of aramchol in its upcoming phase IIb trial in non-alcoholic steatohepatitis patients.

IN THE CLINIC

Immuron Ltd., of Melbourne, Australia, said it secured ethics approval for all six Australian hospitals participating in its clinical studies testing IMM-142E in non-alcoholic steatohepatitis. The placebo-controlled, double-blind and dose-ranging studies will treat patients for six months.

Momenta Pharmaceuticals Inc., of Cambridge, Mass., said a clinical trial application to start a trial for M923, a biosimilar version of Humira (adalimumab, Abbvie Inc.), has been accepted by the UK Medicines and Healthcare Products Regulatory Agency. That development triggers two milestones, with an aggregate payment of $12 million, under the collaboration with **Baxter International Inc.**, of Deerfield, Ill. (See *BioWorld Today*, Dec. 28, 2011.)

Oncomed Pharmaceuticals Inc., of Redwood City, Calif., said patient dosing started in the randomized, placebo-controlled phase II portion of the company's PINNACLE study of anti-Notch 2/3 cancer stem cell antibody tarextumab (OMP-59R5) in small-cell lung cancer (SCLC). Tarextumab is being studied in combination with chemotherapy in patients with previously untreated, extensive-stage SCLC, and the trial will compare progression-free survival (PFS) outcomes. Additionally, PFS will be assessed using a predictive biomarker for high tumor Notch3 expression. About 130 patients are expected to be enrolled.

Otonomy Inc., of San Diego, said it achieved target enrollment in its phase IIb trial of steroid candidate OTO-104 in patients with Meniere's disease. The randomized, double-blind, placebo-controlled study recruited a total of 140 patients, who will be observed for up to four months following a single intratympanic injection of either OTO-104 or placebo. The primary endpoint, consistent with the previous phase Ib trial, is the reduction in vertigo frequency during month three following treatment, compared to a one-month baseline period. The trial was designed to serve as one of two pivotal, single-dose efficacy trials that the company expects the FDA will require for a new drug application in Meniere's.

TG Therapeutics Inc., of New York, said it initiated a multicenter, phase I trial to evaluate the safety and efficacy of the combination of TGR-1202 and Imbruvica (ibrutinib, Pharmacyclics Inc. and Johnson & Johnson) for patients with relapsed and/or refractory chronic lymphocytic leukemia and mantle cell lymphoma. This is the first trial evaluating the "all-oral" combination of TGR-1202, the company's once per day, PI3K delta inhibitor with ibrutinib, the FDA-approved oral Bruton's tyrosine kinase inhibitor. The study is being conducted in collaboration with the Blood Cancer Research Partnership and Dana-Farber Cancer Institute.

Tracon Pharmaceuticals Inc., of San Diego, said it initiated dosing in the phase II portion of a study testing TRC105 in combination with Inlyta (axitinib, Pfizer Inc.), a vascular endothelial growth factor (VEGF) inhibitor, to treat patients with renal cell carcinoma. The study is expected to enroll about 150 patients and will measure progression-free survival as the primary endpoint. TRC105, an anti-endoglin antibody, is being studied in multiple clinical trials in combination with agents that inhibit angiogenesis by targeting the VEGF pathway.

Unum Therapeutics Inc., of Cambridge, Mass., said it started the first trial testing its ATTCK20 therapy, which combines a patient's antibody-coupled T-cell receptor T cells administered with Rituxan (rituximab, Biogen Idec Inc. and Roche AG), a monoclonal antibody targeting CD20. The phase I study will examine the feasibility, safety and potential efficacy of infusing the ATTCK20 combination therapy in patients with B-cell malignancies and persistent disease following standard therapy. The company launched earlier this year. (See *BioWorld Today*, Oct. 22, 2014.)

Zogenix Inc., of San Diego, said long-term phase III data published in the *Journal of Pain Research* showed that the safety and tolerability of Zohydro ER observed in the study was consistent with the phase III pivotal efficacy trial and is comparable to data from other opioid analgesics. Effectiveness, a secondary endpoint, showed the majority (55 percent) of subjects treated with Zohydro ER dosed every 12 hours for up to one year had a clinically meaningful improvement in pain scores (≥ 30 percent reduction in average daily pain intensity). Secondary outcomes also demonstrated improvements in function, depression and anxiety assessments.

PHARMA: OTHER NEWS TO NOTE

Contera Pharma ApS, of Copenhagen, said **Bukwang Pharmaceutical Co. Ltd.**, of Seoul, South Korea, acquired 100 percent of Contera Pharma from its current shareholders. The shareholders received an undisclosed up-front payment and are entitled to future contingent and royalty payments. Contera's lead product is JM-010, which is in development for treating levodopa-induced dyskinesia.

CSL Behring, of King of Prussia, Pa., said the Centers for Medicare & Medicaid Services extended the new technology add-on payment for Kcentra (prothrombin complex concentrate [human]) through September 2015 for eligible Medicare beneficiaries treated in the inpatient hospital setting. Kcentra is a non-activated 4-factor prothrombin complex concentrate indicated for the urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist therapy in adult patients with acute major bleeding or in need of an urgent surgery or invasive procedure.

Ipsen Biopharmaceuticals Inc., of Basking Ridge, N.J., said the FDA accepted for review its supplemental biologics license application for Dysport (abobotulinumtoxinA) for the treatment of upper limb spasticity in adult patients. Dysport is approved in the U.S. for treating adults with cervical dystonia and has been cleared in other markets for upper limb spasticity.

Pfizer Inc., of New York, said it completed the acquisition of Deerfield, Ill.-based **Baxter International Inc.**'s portfolio of marketed vaccines. As previously announced, Pfizer also acquired a portion of Baxter's facility in Orth, Austria, where those vaccines are manufactured.

PHARMA: OTHER NEWS TO NOTE

Takeda Pharmaceutical Co. Ltd., of Osaka, Japan, said the FDA granted breakthrough therapy status to its oral proteasome inhibitor, ixazomib (MLN9708), for the treatment of relapsed or refractory systemic light-chain (AL) amyloidosis. The company is in phase III testing – a trial dubbed TOURMALINE-AL1 – with ixazomib plus dexamethasone in patients with relapsed or refractory AL amyloidosis.

PHARMA: IN THE CLINIC

Concordia Healthcare Corp., of Toronto, said the first North American site began enrolling patients in its phase III trial called OPUS, an open-label, multicenter, randomized study to test photodynamic therapy with Photofrin (porfimer sodium) for injection as a treatment for unresectable, advanced perihilar cholangiocarcinoma Bismuth type III/IV, a rare type of bile duct cancer. OPUS is being conducted under a special protocol assessment agreement with the FDA.

Eli Lilly and Co., of Indianapolis, and **Astrazeneca plc**, of London, said they enrolled the first patient in the phase II/III AMARANTH study of oral beta secretase cleaving enzyme inhibitor AZD3293 (LY3314814). The pivotal study will investigate the safety and efficacy of AZD3293/LY3314814 compared with placebo in the treatment of early Alzheimer's disease. The study, which has a two-year treatment period, aims to enroll more than 1,500 patients.

Hovione, of Lisbon, Portugal, said it filed its first investigational new drug application with the FDA for minocycline gel, a formulation using a new crystalline base form of minocycline, to administer topically for acne.

Novartis AG, of Basel, Switzerland, updated the phase III study of fingolimod in primary progressive multiple sclerosis (MS), stating that the study did not meet the primary endpoint. Data from the INFORMS trial showed no significant difference between fingolimod and placebo on a combination of disability measures. Fingolimod, marketed as Gilenya, is approved in the U.S. for first-line treatment of relapsing forms of MS in adults. In Europe, Gilenya is indicated for adult patients with highly active relapsing-remitting MS (RRMS) defined as either high disease activity despite treatment with at least one disease-modifying therapy or rapidly evolving severe RRMS.

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