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'The better half of ketoconazole'

SONICS boom: Strongbridge eyes filing on first Cushing's phase III data

By Marie Powers, News Editor

Officials from Strongbridge Biopharma plc plan to make their case to the FDA about the potential for an accelerated approval pathway for Recorlev (levoketoconazole) to treat endogenous Cushing's syndrome after the open-label, single-arm SONICS study achieved statistical significance on the pre-specified primary endpoint.

See Strongbridge, page 3

Paratek's adcom debut ends with positive votes for first-in-class CABP, ABSSSI treatment

By Mari Serebrov, Regulatory Editor

Weighing a mortality imbalance in one clinical trial with the need for new antibacterials amid growing drug resistance, the FDA's Antimicrobial Drugs Advisory Committee gave its support Wednesday for the approval of Paratek Pharmaceuticals Inc.'s omadacycline, the first of a new generation of tetracycline drugs known as aminomethylcyclines.

The committee voted 17-1 in support of omadacycline as a treatment for acute bacterial skin and skin structure infections (ABSSSI) and 14-4 for its approval in community-acquired bacterial pneumonia (CABP). That support came with recommendations for required studies powered to determine whether a mortality imbalance seen in the CABP trial was the bad luck of the draw or a true safety signal in older, sicker patients with co-morbidities.

The major difference between

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Cell therapy, gene therapy, drugs

Amphibious Ambys draws $140M; fights on land, sea for liver regenerative bids

By Randy Osborne, Staff Writer

Ambys Medicines Inc. interim CEO Jeff Tong said the firm's unusual combination of the $60 million series A financing with a deal enlisting Takeda Pharmaceutical Co. Ltd. to the tune of

See Ambys, page 5

The BioWorld Biome

Repair, not deletion

Embryo editing success confirmed, though not ready for prime time

By Nuala Moran, Staff Writer

LONDON – Scientists at the Oregon Health and Science University (OHSU) have produced new evidence that gene editing human embryos activates an inherent DNA repair mechanism, leading a mutant paternal gene to be replaced with a newly minted maternal copy.

After first reporting they had applied the technique to repair the MYBPC3 gene that causes hypertrophic cardiomyopathy, the researchers have now successfully corrected two other mutations that also are causes of the frequently fatal inherited heart condition.

The research is a rebuff to doubters, including eminent geneticist George Church, of Harvard Medical School, and Allan Bradley, director emeritus of the Sanger Center in Cambridge,

See Gene editing, page 7

South Korea's ABL Bio buys bispecific antibodies from I-Mab in $100M deal

By David Ho, Staff Writer

HONG KONG – China's I-Mab Biopharma Co. Ltd. entered a strategic partnering agreement with ABL Bio Inc., of South Korea. I-Mab will out-license its bispecific antibody (BsAb) for an undisclosed target to ABL Bio for about $100 million.

See I-Mab, page 6

Kyowa Hakko Kirin's Poteligeo cleared by FDA for mycosis fungoides, Sezary syndrome

From staff reports

Kyowa Hakko Kirin Co. Ltd. is expected to begin commercializing its CCR4-targeting monoclonal antibody in the U.S. in the fourth quarter, after winning the FDA's nod Wednesday for use in two types of non-Hodgkin's lymphoma, including

See Poteligeo, page 8

Newco News

Singapore biotech Dotbio hits the spot with $2.3M seed financing for I-O play

By David Ho, Staff Writer

HONG KONG – Singaporean biotech startup Dotbio Pte. Ltd. launched this week with seed capital of $2.3 million. The new player on the biotech scene is focused on the development of immuno-

See Dotbio, page 9

Other news to note

Agilent Technologies Inc., of Santa Clara, Calif., said its PD-L1 IHC 22C3 Pharmdx assay is now labeled for an updated use in urothelial carcinoma in Europe. EU doctors can now use the test as an aid to identify urothelial carcinoma patients who are ineligible for cisplatin and may respond to Keytruda (pembrolizumab, Merck & Co. Inc.) as a first-line treatment option.

Astrazeneca plc, of Cambridge, U.K., has agreed to pay $110 million to the state of Texas to settle lawsuits alleging that the company falsely and misleadingly marketed Seroquel (quetiapine) and Crestor (rosuvastatin) in violation of the Texas Medicaid Fraud Prevention Act. The company was accused of engaging in false and misleading marketing schemes at a time when it was under obligations of a 2010 federal corporate integrity agreement resulting from prior allegations of Medicaid fraud, the Texas Attorney General's office said.

Context Therapeutics LLC, of Philadelphia, said it has signed multiple academic research collaborations to further understand the role of progesterone receptor signaling and its blockade to overcome resistance mechanisms underlying metastatic breast cancer. The agreements include experts at the University of Minnesota, Baylor College of Medicine, Memorial Sloan Kettering Cancer Center, the University of Chicago and Northwestern University. Context is developing Apristor (onapristone extended release), a phase II candidate for progesterone receptor-positive metastatic breast cancers.

Collplant Holdings Ltd., of Ness Ziona, Israel, a regenerative medicine company using plant-based recombinant human collagen technology for tissue repair products, is voluntarily delisting its ordinary shares and series I warrants and series K warrants from trading on the Tel Aviv Stock Exchange. The company's American depositary shares (NASDAQ:CLGN), each of which represents 50 ordinary shares, will continue to trade on Nasdaq.

Insys Therapeutics Inc., of Phoenix, has reached an agreement in principle with the U.S. Department of Justice to settle the DoJ's civil and criminal investigation into inappropriate sales and commercial practices by some former company employees. The agreement calls for Insys to pay $150 million over five years, with the potential for contingency-based payments of up to $75 million associated with certain events. A final settlement would include other material nonfinancial terms and conditions, which will also be subject to negotiation, the company said. The agreement remains subject to negotiation of final settlement documents with the government. Company shares (NASDAQ:INSY) rose $1.14, or about 17.1 percent, to close at $7.79 on Wednesday.

Nevakar Inc., of Bridgewater, N.J., said it recently entered an exclusive licensing agreement with Dublin-based **Endo International plc**'s subsidiary, Endo Ventures Ltd., for the development of five sterile injectable products in the U.S. and Canada. Pursuant to the agreement, Nevakar will develop and seek FDA approval for the products, and Endo's Par Pharmaceutical Sterile Products division will launch and distribute the products upon approval.

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Strongbridge

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Strongbridge, of Trevose, Pa., reported that 30 percent of individuals in the initial pivotal phase III trial achieved normalization of mean urinary free cortisol (UFC) following six months of maintenance treatment with Recorlev without a dose increase (p<.025, confidence interval [CI]: 21 percent, 40 percent). A sensitivity analysis of the primary endpoint showed that 38 percent (CI: 28 percent, 49 percent) of participants achieved UFC normalization regardless of dose increase. The company also said that 76 percent of the 55 maintenance completers with both baseline and month six data showed UFC reduction of 50 percent or greater from baseline.

In addition, individuals treated with Recorlev showed statistically significant and clinically meaningful improvements from baseline (p<.0001) across key secondary endpoints of cardiovascular risk, including fasting blood glucose, hemoglobin A1C, total cholesterol, low-density lipoprotein-cholesterol, body weight and body mass index.

In terms of safety and tolerability, based upon data collected through the study's six-month maintenance phase, 10.6 percent of individuals enrolled in SONICS showed an increase in alanine aminotransferase (ALT) measurement of greater than three times the upper limit of normal (ULN), but a much smaller group – 3.2 percent of enrolled participants – rose to the level of greater than five times the ULN. The company said 7.4 percent of SONICS enrollees had liver-related adverse events (AEs) defined in the protocol as an "AE of special interest" but no severe drug-induced liver injury, Hy's law, transaminases greater than 20 times ULN or obvious dose relationship was seen, although exposure relationship analyses were pending.

Twelve patients (12.8 percent) discontinued treatment due to adverse events (AEs). For the two most commonly reported AEs, no patients discontinued treatment due to nausea and one patient discontinued due to headache. Other commonly reported (greater than 15 percent) treatment-emergent AEs included peripheral edema, hypertension, fatigue, diarrhea and increased ALT.

Fourteen patients (14.9 percent) reported one or more serious AEs; four were deemed by investigators as related to the study drug. On a call with analysts, Matthew Pauls, president and CEO, declined to provide details of the SAEs, citing the company's intention to report full data from SONICS at an upcoming medical meeting, possibly as early as the fourth quarter.

One patient death, from colon cancer, was reported during the study but was considered unrelated to Recorlev.

"The tolerability is very good in this study," observed Fred Cohen, Strongbridge's chief medical officer. "We only had just over 12 percent discontinuations due to an adverse event. In my experience, for a disease of this scale, that's remarkable."

Pauls called the findings a "momentous" achievement for Strongbridge and the Cushing's syndrome community. Investors seemed to agree, propelling the company's shares (NASDAQ:SBBP) to a gain of $1.40, or more than 31 percent, Wednesday to close at $5.90. Approximately 10.5 million shares traded hands, or nearly 28 times the stock's three-month moving average.

SONICS, which enrolled 94 individuals with Cushing's at centers in North America, Europe and the Middle East, involved three treatment phases. In the dose-titration phase of two to 21 weeks, participants started Recorlev at 150 mg twice daily and titrated in 150 mg increments to a maximum of 600 mg twice daily until a therapeutic dose resulting in UFC normalization was achieved. During the six-month maintenance phase, designed to maintain UFC normalization, participants remained on a fixed dose that was not changed other than for safety reasons or loss of efficacy. UFC response rate was measured and recorded at the end of the maintenance period to compile data for the primary efficacy analysis. Participants then entered the extended evaluation phase for another six months.

> *"We have a case to make, and we're going to take it to the FDA.*
>
> Fred Cohen
> CMO, Strongbridge Biopharma

Patients were deemed UFC responders in SONICS if they completed the maintenance phase, recorded normal (at or below the ULN) mean 24-hour UFC on the basis of at least two (and up to four) adequate 24-hour urine samples and had no increase in Recorlev dosage throughout the maintenance phase. Additionally, patients with a recent history of pituitary radiation were required to show a rebound increase in mean UFC above the ULN following a two-week minimum withdrawal of Recorlev at the end of the maintenance period.

Strongbridge reported that 77 of the 94 patients enrolled in SONICS entered and 61 patients completed the maintenance phase. Many of those enrolled were diagnosed with co-morbidities that included diabetes (38 percent), hypertension (71 percent) and hypercholesterolemia (36 percent). Pauls said the company was just beginning to conduct analyses of Recorlev on those subgroups.

A second pivotal phase III, dubbed LOGICS, continues to recruit participants. The double-blind, placebo-controlled, randomized study plans to enroll 35 participants treated with Recorlev during SONICS to assess the effect of withdrawal to placebo compared to continued treatment, based on the cortisol therapeutic response established during open-label therapy. Top-line data are expected in the first quarter of 2019.

But Strongbridge isn't waiting for those findings to seek a parlay with the FDA.

"The top-results of the SONICS study suggest that Recorlev is an effective and well-tolerated cortisol synthesis inhibitor in Cushing's syndrome," Cohen said, calling data on the FDA orphan drug-designated candidate "compelling."

He added, "We look forward to discussing the SONICS data with the FDA and the potential for an accelerated approval pathway for Recorlev," while discussions with ex-U.S. regulators continue. "We have a case to make, and we're going to take it to the FDA."

'Potential to become a first-line treatment'

The SONICS data supported Strongbridge's long-term view that Recorlev – an 2S,4R enantiomer of ketoconazole that's

See Strongbridge, page 8

Adcom

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the yes and no votes was the timing of such a follow-up study. Panelists voting yes were comfortable with postmarket studies; those voting no wanted the question resolved before approval.

There were eight, or 2.1 percent, deaths in the omadacycline group, and three, or 0.8 percent, in the moxifloxacin comparator arm in the OPTIC study, the only phase III trial in CABP. Ahead of the meeting, the FDA noted that the rate of mortality in the omadacycline group was similar to the 30-day mortality observed in other recently conducted CABP trials, and none of the deaths could be directly linked to the study drug. (See *BioWorld*, Aug. 7, 2018.)

A similar imbalance wasn't seen in the two ABSSSI trials, which compared omadacycline with linezolid. In those trials, the 30-day mortality included one death – resulting from an overdose of an illicit drug – in the omadacycline arm and two cardiac-related deaths in the comparator group. In general, the patients in the ABSSSI trials were younger and had fewer co-morbidities than those in the CABP trial. But there's also a possibility that moxifloxacin has a lower mortality rate than linezolid and other commonly used antibacterials.

The features that make omadacycline a promising new antibiotic added to the safety concerns for one of the panelists. A once-daily broad-spectrum antibiotic that can be administered via I.V. or orally, omadacycline doesn't have the resistance issues of older tetracyclines and it has shown a low propensity for *Clostridium difficile* infections.

The convenience of the drug would make it an attractive choice for doctors, so it could become the go-to antibiotic despite the safety issues, said Joanna Schaenman, an associate clinical professor in the Division of Infectious Diseases at the University of California-Los Angeles' David Geffen School of Medicine. That's why she voted against approval for both indications.

If future studies show the CABP mortality imbalance was due to chance, omadacycline would be a "wonderful drug," Schaenman said, adding that it holds "real promise."

Should the FDA approve the drug before a further safety study is done, it should require the safety concerns to be spelled out in the labeling, Schaenman and other panelists advised.

Another concern voiced at the meeting was the demographics of the study population. Although the trials had sites in the U.S and several other countries, the majority of the participants were from sites in Eastern Europe. As a result, 80 percent of the study population was white. Sumathi Nambiar, director of the FDA's Division of Anti-Infective Products, said it's typical for anti-infective trial sites to be in Eastern Europe, because it's difficult to get sites in the U.S. and other parts of Europe.

One step closer

While Paratek welcomed the committee's support, it has no time to waste sitting on its laurels. "Today's recommendations from the advisory committee move us one step closer to making this important new treatment option available to patients and physicians," Paratek Chairman and CEO Michael Bigham said, adding that he looks forward to working with the FDA as it completes its review over the next few months. The PDUFA date is in October.

If the agency follows the committee's recommendations, the Boston-based startup will have plenty of new challenges as it prepares to commercialize its first drug and work through reimbursement and pricing issues while designing an adequate follow-up program and continuing an ongoing study of omadacycline in cystitis. (Besides granting omadacycline priority review and fast track status, the FDA designated it as a qualified infectious disease product for ABSSSI, CABP and complicated urinary tract infections.)

Paratek also is preparing an EU marketing authorization application for omadacycline, and the drug is being studied against pathogenic agents such as plague and anthrax under a research agreement with the U.S. Department of Defense.

Developing and getting approval of a new anti-infective is only part of the battle. Another big issue is reimbursement after the drug's been approved, Evan Tzanis, Paratek's chief development officer, told *BioWorld*. With antibiotics the No. 1 cost for hospitals, cost savings is important, he added. A reimbursement system that favors cheaper generics of older drugs and the need to reserve new agents for emerging resistance further complicate the space.

Although omadacycline was developed as a first-line antibiotic, the growing threat of multiple drug-resistant drugs means it should be reserved for use in geographies where resistance is an issue, Tzanis said.

Ben Strain, executive director and head of investor relations and corporate communications at Paratek, added that if a cheaper generic antibiotic is available and will work for a given patient, it should be used.

At the same time, Strain noted the value omadacycline could offer. The ability to go from I.V. to an oral dose could shorten hospitalizations or reduce the need for some hospital stays, he told *BioWorld*, adding that Paratek will explore value-based arrangements with hospitals when the drug launches.

Investors reflected the adcom's positivity when trading (NASDAQ:PRTK) resumed after Wednesday's vote with an opening bid of $11.85, up nearly 9 percent from Tuesday's close of $10.90. Paratek shares hit a high of $12.30 amid heavy trading, but the initial euphoria waned with the afternoon. By day's end, Paratek closed at $10.55. ♦

Earnings

Horizon Pharma plc, of Dublin, reported second-quarter net sales of $302.8 million, up 5 percent from its second-quarter 2017 sales of $289.5 million, driven by continued growth of the company's orphan and rheumatology medicines, it said. Revenue from the company's gout drug, Krystexxa (pegloticase), and its urea cycle disorder drug, Ravicti (glycerol phenylbutyrate), led the way, bringing in $57 million and $58.6 million, respectively, in the second quarter. The company said it plans to initiate a new study of Krystexxa to continue exploring a broader clinical profile for the medicine. Horizon narrowed its net losses to $32.8 million during the quarter vs. $209.5 million in the second quarter of 2017. The company had cash and cash equivalents of $710.2 million as of June 30.

Ambys

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$80 million up front came about because venture backer Third Rock, where Tong is a partner, "wanted to make sure that by doing the deal we weren't going to hamper the growth of the company."

Although other firms may have launched with "large[r] up-front checks, they essentially have sold the first product in their pipeline or more, or they've sold some level of corporate governance, or the larger company has a prespecified buyout term," Tong told *BioWorld*. "All those features are really hard to work with when you're trying to build a visionary company from scratch."

Osaka, Japan-based Takeda and Third Rock contributed to the series A for Ambys, of Redwood City, Calif., focused on regenerative medicine for the liver. On the first four programs, Takeda can take ex-U.S. commercialization rights at the time of IND filings, "and then other downstream fees and milestones kick in, and they start sharing with us 50-50 co-funding of the global development program," Tong said. "Third Rock is always looking for areas of disruptive science. For the last couple of years we've been working on merging the science, the clinical, and the business strategy to build a company that is solely liver-focused," because of the huge unmet need in the U.S. and globally.

Ambys has a program in cell therapy, where "we believe the ability to develop fully functional human hepatocytes will be a game-changer," allowing the company to add or remove functionalities, Tong said. There's a gene therapy effort, too, which enjoys the "benefit of 20-plus years of work in the field by many who have come before us," he said. "We can use those tools [developed earlier] but direct them in a different way. Rather than target a monogenic disease where we are simply replacing a protein, we're looking to see if we can use the tools of gene therapy to reprogram cells" for in vivo transcription-factor reprogramming, he said.

Third, Ambys is working on drugs, specifically "small molecules that can complement the loss of a protein that's important to the liver," he said.

"It's a very ambitious R&D agenda," Tong said.

That agenda is led by Chief Scientific Officer Michael Holmes, previously with Sangamo Therapeutics Inc., of Richmond, Calif., where he worked on the company's zinc finger nuclease (ZFN) technology. Sangamo's approach in February drew Foster City, Calif.-based Gilead Sciences Inc.'s Kite Pharma unit to the table for a collaboration, designed to exploit the ZFN platform for the development of next-generation ex vivo cell therapies in cancer. Kite is using ZFN to modify genes and develop new cell therapies for autologous and allogeneic approaches. Under the terms, Sangamo collected an up-front payment of $150 million and is eligible for as much as another $3.01 billion, calculated across 10 or more products deploying ZFN and based on reaching research, development, regulatory and commercialization goals. (See *BioWorld*, Feb. 23, 2018.)

But Ambys' name did not derive from Tong's adjective for the R&D plan. Facing the ever-more daunting challenge of coming up with a way to distinguish their firm, organizers "were thinking about the Mexican salamander, the axolotl – *Ambystoma mexicanum* – which is the most regenerative species known to man," he said. "You can chop off its limbs and they regrow without scarring." They truncated the genus portion of the biological term for the amphibian. (The dictionary name is already taken by another regenerative medicine firm: Phoenix-based Axolotl Biologix Inc., which last fall put on the market its third amniotic allograft product, Axobiofluid A, an ambient amniotic allograft fluid meant as an alternative to the existing cryopreserved Axobiofluid.)

"To be able to prosecute all three programs in parallel is one of the strategic reasons" for the Takeda deal, Tong said. Four co-founders brought "complementary as well as overlapping skill sets to the founding of Ambys. Some of the programs we're working on were initially conceived or inspired by their labs" at Oregon Health and Science University, the Salk Institute for Biological Studies, the University of California, San Francisco, and the University of Illinois.

Pulling together a deal "at this scale, and to do it so early" represents a first for Third Rock as well as Takeda, Tong said. "Several of my colleagues and I have been working on this for the past couple of years." The venture outfit had been "getting very interested in regenerative medicine generally. We hosted an internal conference inviting leading academics and industry folks to brainstorm with us," and Ambys was born earlier this year, he said.

Tong did not provide timing on when any of the efforts might reach phase I experiments, "but the $140 million was designed to enable all three of the program areas to get into the clinic" and provides "at least four or five years of cash runway."

Ambys' staff roster lists about 20, with 10 full-timers. The company aims to grow to 30 by the end of the year. ♦

Earnings

Jazz Pharmaceuticals plc, of Dublin, reported that its total revenues increased by 27 percent in the second quarter of 2018 as compared to the same period in 2017, due to the contributions from sales of Xyrem (sodium oxybate), Erwinaze/Erwinase (asparaginase *Erwinia chrysanthemi*), Defitelio (defibrotide) and the addition of Vyxeos (cytarabine/daunorubicin) following that product's launch in August 2017. Total second-quarter revenue was $500.5 million vs. $394.4 million in the second quarter of 2017. Net income for the second quarter was $92.3 million, or $1.50 per share, vs. $105.6 million, or $1.72 per share, for the second quarter of 2017, reflecting an impairment charge of $42.9 million resulting from the company's decision to sell its rights related to the severe chronic pain management drug Prialt (ziconotide) to **Tersera Therapeutics LLC**, of Lake Forest, Ill. As of June 30, Jazz had cash, cash equivalents and investments valued at $815.1 million.

I-Mab

Continued from page 1

"For the global out-licensing agreement, ABL will have the rights, excluding greater China, to develop and commercialize that BsAb for all indications with a primary focus on oncology," Raven Lin, vice president of corporate development at I-Mab, told *BioWorld*.

Under the terms of the agreement, ABL Bio will pay $2.5 million up front. Shanghai-based I-Mab will also receive research and development, regulatory and sales-based milestone payments, which could result in aggregate payments of $100 million. In addition, ABL Bio will pay tiered royalties on net sales.

Perhaps more significantly, the two companies agreed to collaborate on and co-develop three more bispecific antibody projects as part of the partnership.

"Both I-Mab and ABL will contribute certain sequences and utilize ABL's technology platform to form different pairs of bispecific antibodies. But we are not able to disclose specific targets at the moment. We will pursue all indications but most likely to focus on oncology primarily," said Lin.

"I-Mab and ABL Bio will share rights in China, South Korea and rest of the world in different configurations. Under these collaborations, the two companies will also share the development cost and are entitled to sharing of economic interests," Lin added.

"This partnership with ABL Bio is a latest addition to our growing portfolio of global partnerships spanning from early stage projects to clinical assets," said Jingwu Zang, the founder and CEO of I-Mab. He went on to praise ABL Bio for the firm's "cutting-edge discovery and antibody engineering platform for novel therapeutic antibodies."

Prior to the out-licensing deal with ABL Bio, I-Mab had completed a string of in-licensing deals with global pharmaceutical companies such as Morphosys AG and Genexine Inc. to enrich its China portfolio.

Last December, I-Mab entered a $548 million licensing agreement with Genexine, also from South Korea, for the latter's immuno-oncology drug, Hyleukin, which is designed to reconstitute and enhance antitumoral T-cell immunity. (See *BioWorld*, Jan. 3, 2018.)

In November, I-Mab received the exclusive rights to German firm Morphosys' investigational drug, MOR-202, a human Hucal antibody directed against CD38, a highly expressed and validated target in multiple myeloma.

With an eye on innovative biologic therapies, I-Mab also purchased a recombinant protein inhibitor of the interleukin-6 pathway, olamkicept, from Swiss company Ferring Pharmaceuticals SA in 2016. (See *BioWorld Today*, Dec. 30, 2016.)

"Bispecific antibody truly represents the next wave biologics in cancer immunotherapy for its unique modality to create target synergy," Zang said.

I-Mab raised series B financing of $150 million in 2017. In June, it added another $220 million in one of the largest series C financing on the Chinese biotech scene.

The third round of financing was led by Hony Capital, with participation from Hillhouse Capital, Hopu Investments, CDH Investment, Ally Bridge Group, Singapore-based EDBI, and existing investors C-Bridge Capital and Tasly Capital.

"I-Mab has made remarkable progress in delivering company and project milestones as well as assembling a world class team," said Wei Fu, founding partner of C-Bridge Capital.

"In a very short time, I-Mab has built a globally competitive pipeline and a highly experienced team to deliver the pipeline milestones. This round of financing will facilitate further development of our innovative assets in China and internationally," said Zang of the latest round of financing.

Currently, I-Mab has more than 10 investigational drugs under development.

According to the company, it has already submitted several IND applications and is prepared to submit additional INDs in order to initiate clinical trials in China and the U.S., including multiple phase II and phase III studies.

I-Mab was born from a merger between Third Venture Biotech and Tasgen Bio-tech Co. Ltd. and aims to be an end-to-end fully integrated biopharma company.

"We are developing immune-oncology and immune-inflammation treatments that have the potential to be first-in-class and best-in-class drugs," said Lin.

Lin revealed that the company is actively seeking co-development and licensing partnerships for multiple therapeutic areas in endocrine disorders, metabolic disease, autoimmune disease and oncology.

I-Mab also recently appointed former managing director and Asia head of health care investment banking and capital markets at investment bank Jefferies, Jielun Zhu, as its chief financial officer. ♦

Regulatory front

The U.S. **Department of Health and Human Services** (HHS) and the **Centers for Medicare & Medicaid Services** (CMS) said CMS will begin providing Medicare Advantage plans as part of the Trump administration's Patients First blueprint, allowing for the use of tools employed by private sector insurers to negotiate lower prescription drug prices for patients. Medicare Advantage plans, which provide Medicare benefits to roughly 20 million beneficiaries – a third of all beneficiaries in Medicare – will have the option of negotiating for Part B drugs. And Medicare Advantage Plans that also offer a Part D benefit will be allowed to cross-manage across both Parts B and D. "By allowing Medicare Advantage plans to negotiate for physician-administered drugs like private sector insurers already do, we can drive down prices for some of the most expensive drugs seniors use," said HHS Secretary Alex Azar. Medicare Advantage plans can begin using those tools as part of their 2019 policies and, beginning in 2020, plans will be able to pass on savings to patients through lower premiums. In 2017, Medicare Advantage plans spent $11.9 billion on Medicare Part B drugs.

Gene editing

Continued from page 1

U.K., who questioned the MYBPC3 correction claim, saying it was biologically impossible. Physical separation of parental genomes in paternal and maternal pronuclei in early zygotes would prevent such directed repair, they say.

Rather than correcting MYBPC3, editing out the paternal gene introduced a large deletion which was not picked up by the genetic assay used by the OHSU team, the critics said.

The criticisms followed a landmark paper published a year ago, in which the OHSU researchers, led by Shoukhrat Mitalipov, director of the university's Center for Embryonic Cell and Gene Therapy, reported a 72.4 percent success rate in correcting the MYBPC3 gene, by introducing a CRISPR gene editing construct at the point of in vitro fertilization. (See *BioWorld Today*, Aug. 3. 2017.)

In the face of the criticisms, Mitalipov has gone back and re-tested the embryonic samples generated in the MYBPC3 study. Writing in *Nature*, he describes the verification process and cites additional research to bolster the central finding that a precisely targeted break in the mutant DNA is repaired by copying the genetic code of the normal gene from the second parent as a template.

"We had all the samples still frozen … so we could look for larger deletions. We didn't find any single case of wider deletions: all our conclusions were right," Mitalipov said in a teleconference. "It was indeed gene repair, not loss of the mutant gene."

He also ruled out another possibility raised by critics, that the early stage embryos developed through parthenogenesis, without a genetic contribution from sperm, after checking that the embryos contained both maternal and paternal genes.

Mitalipov also claimed to have replicated the original findings in two other mutations that cause hypertrophic cardiomyopathy. "We looked at the repair response of two other genes. We've seen a similar response, with a high frequency of repair," he said.

That aspect of the research is not covered in Mitalipov's peer-reviewed communication in the Aug. 8, 2018, online issue of *Nature*, which was published alongside two critiques of his original study.

Mitalipov and colleagues "provide some compelling data" to indicate they had obtained repair of a mutant allele coming from the father via the use of maternal DNA as a template, said Robin Lovell-Badge, group leader at the Francis Crick Institute in London.

However, they fail to provide an explanation of why the maternal template was used for the repair, rather than the exogenous DNA template administered as part of the CRISPR construct, he noted.

"There are still too many unknowns and this just emphasizes that we are not yet ready to use genome editing methods in the early embryo for 'real,' to avoid having a child with a genetic disease," Lovell-Badge said.

Many questions remain concerning the precise mechanisms,

> *"There are still too many unknowns and this just emphasizes that we are not yet ready to use genome editing methods in the early embryo for 'real'.*
>
> Robin Lovell-Badge
> Francis Crick Institute in London

agreed Mitalipov. In addition, it is necessary to increase the efficiency of the process. "It is unacceptable for clinical application now. We need to get to 90 – 100 percent efficiency," Mitalipov said.

Since publication of the original research, the same phenomenon has been shown to operate in tomatoes and in mice, indicating the mechanism is conserved. "Independent replication of our work provides additional evidence that our discovery may lead to the prevention of inherited disease," Mitalipov said.

"Given that such DNA repair seems to be widely conserved across different species, in-depth mechanistic studies can potentially be addressed in model organisms," said Mitalipov, calling for the endogenous repair mechanism to be further explored, reproduced in other mutations and "perhaps evaluated" in germline gene editing for therapeutic applications.

If the effect is confirmed, using CRISPR to remove a mutant gene and trigger the endogenous repair mechanism could be applied to more than 10,000 single gene inherited disorders that currently affect an estimated 600 million people worldwide.

At the same time, Mitalipov said he intends to hone the DNA introduced by CRISPR, with the aim of treating inherited diseases with a maternal and paternal component. "For homozygous mutations you clearly need a synthetic gene that will be copied. It doesn't really work so far; the exogenous template is not recognized as real," he said. ♦

Poteligeo

Continued from page 1

Sezary syndrome (SS), for which it becomes the first approved therapy.

Branded Poteligeo (mogamulizumab-kpkc), the drug received orphan and breakthrough therapy designations and was granted priority review. The agency extended the original early June PDUFA by three months to Sept. 4.

Approval covers the use of Poteligeo injection for adults with relapsed or refractory mycosis fungoides (MF) or SS after at least one prior systemic therapy, and was based on progression-free survival (PFS) data from the pivotal MAVORIC study involving 372 patients with histologically confirmed MF or SS who had failed at least one systemic therapy. MAVORIC tested mogamulizumab against vorinostat, an HDAC inhibitor marketed as Zolinza by Merck & Co. Inc. that is indicated to treat cutaneous manifestations in patients with cutaneous T-cell lymphoma (CTCL) who have progressed after two systemic therapies.

Results showed investigator-assessed PFS of 7.7 months in the mogamulizumab arm vs. 3.1 months in the vorinostat arm ($p<0.0001$), while independent review of PFS benefit was 6.7 months vs. 3.8 months, respectively ($p=0.0007$). An overall response rate (ORR) of 28 percent was seen in the mogamulizumab arm vs. 4.8 percent for patients on vorinostat ($p<0.0001$). By disease subtype, the ORR was 21 percent vs. 7.1 percent for patients with MF ($p=0.0042$) and 37 percent vs. 2.3 percent for patients with SS ($p<0.0001$).

MF and SS are the two most common type of CTCL, with MF accounting for 50 percent to 70 percent of all cases and SS accounting for about 3 percent. Both are characterized by localization of malignant T lymphocytes to the skin, though SS is the more aggressive, leukemic form of CTCL.

Mogamulizumab was developed using Tokyo-based Kyowa Hakko Kirin's Potelligent platform, which is designed to increase the antibody-dependent cellular cytotoxicity by reducing the amount of fucose in the sugar chain structure of the compound. The most common side effects from treatment included rash, infusion-related reactions, fatigue, diarrhea, musculoskeletal pain and upper respiratory tract infection.

Mogamulizumab was first approved in Japan in 2012 for other hematological malignancies and in 2014 for use in CTCL. It currently is undergoing review in Europe. ♦

Strongbridge

Continued from page 3

been deemed a new molecular entity – "is the better half of ketoconazole for treating Cushing's syndrome," Pauls added.

The rare, potentially fatal endocrine disease is caused by chronic elevated cortisol exposure. Common symptoms include weight gain or obesity, fatigue, muscle weakness, headaches, mood or sleep disturbances, facial rounding or redness, excess body hair growth in women or baldness in men, easy bruising and other skin changes. Patients often develop new or worsening high blood pressure, abnormal levels of blood lipids and abnormal blood glucose or diabetes.

Qualitative and quantitative research conducted by the company suggested a large unmet medical need in the indication, Pauls said, "given the limited number and utility of currently FDA-approved treatments and the deficiencies of off-label treatments."

Two other drugs are approved in the U.S. to treat Cushing's: Signifor (pasireotide, Novartis AG), injected subcutaneously twice daily, and oral Korlym (mifepristone, Corcept Therapeutics Inc.). Signifor, though, has been associated with hyperglycemia. Korlym has a potential for vaginal bleeding and endometrial changes; its active ingredient is better known as RU-486.

Additionally, three drugs – ketoconazole, metyrapone and cabergoline – are used off-label in the U.S., although ketoconazole, approved in the EU to treat Cushing's, is known to cause liver toxicities.

"If approved, Recorlev has the potential to become a first-line treatment for patients newly diagnosed with Cushing's syndrome and also could be used for patients who are not adequately controlled or are dissatisfied with their current treatment," Pauls said.

Earlier this year, Strongbridge was issued a patent that will be active until the first part of 2026, not counting extensions, related to Cushing's treatment. The first Recorlev patent, issued in December 2015 and expiring at the end of 2030, covers methods of reducing C-reactive protein levels and inflammation through a once-daily dose. (See *BioWorld*, April 23, 2018.)

Strongbridge, which also reported second-quarter earnings on the call, said Macrilen (macimorelin), its oral ghrelin receptor agonist approved last year to diagnose adult growth hormone deficiency, was launched at the end of July at a wholesale acquisition cost of $4,500 per unit – a price point "about double" what the company expected, Pauls acknowledged.

"What became very apparent in this deep rich market research that we did was that payers and physicians clearly saw and acknowledged that Macrilen is arguably disruptive technology and fulfilling a significant need in the adult growth hormone deficiency market," he said.

Strongbridge also disclosed second-quarter net sales of $4.3 million for Keveyis (dichlorphenamide), approved by the FDA in April 2017 to treat primary periodic paralysis, a spectrum of rare, chronic, genetic, neuromuscular disorders. Management projected full-year 2018 Keveyis revenues of $18 million to $20 million.

Strongbridge reported $85.5 million in cash and equivalents and $87.4 million in outstanding debt as of June 30, compared to $57.5 million in cash and equivalents and $40.8 million in debt as of Dec. 31, and said the combination of cash resources and potential borrowings under its existing credit facility will provide sufficient resources to move Recorlev to potential U.S. approval and launch. The drug's five-year consensus forecast calls for approximately $113 million in sales, according to Cortellis Competitive Intelligence. ♦

Dotbio

Continued from page 1

oncology drugs based on humanized domain antibodies.

The independent biotechnology company was spun out from Singapore's Nanyang Technological University (NTU) and was incorporated in the Southeast Asian city state last June. The seed financing was led by the Heungkong Group via Futec Biomedical Investments Ltd.

Dotbio aims to develop a broad pipeline of drug candidates for new oncology treatments based on its Dotbody technology.

"The domain therapeutic antibody [Dotbody] technology was developed by Dotbio using our Cofi and Hot Cofi screening technologies," Ignacio Asial, founder and CEO of Dotbio, told *BioWorld*. "The Cofi and Hot Cofi technologies allowed us to generate a very stable, low-aggregation scaffold based on the humanized VH [heavy chain variable] domain of Herceptin."

The Dotbody domain therapeutic antibodies are multispecific, humanized and highly stable.

Dotbio has phage display libraries based on the Dotbody scaffold, from which the therapeutic candidates are isolated.

"These Dotbodies against different therapeutic targets can be easily combined into multispecific formats by simply 'connecting the dots' at the DNA level," said Asial. "This significantly simplifies the process of generating multitargeted therapies, reducing development times and costs."

According to Dotbio, domain antibodies exhibit superior tumor penetration as a result of their small size and can be used as building blocks for multispecific antibodies. Dotbodies are optimized by a proprietary technology that improves antibody stability, reduces aggregation and lowers the risk of immunogenicity – increasing the probability of their success in clinical trials.

"Multispecific domain antibodies offer a more refined means to activate the antitumor immune response and to minimize adverse effects as compared to standard antibody-based combination therapies," said Pär Nordlund, co-founder of Dotbio. Nordlund said he believes the company's domain antibody technology would position it as a leader in next-generation multispecific cancer therapies.

The higher stability and small size of Dotbodies also make them highly modular, allowing rapid optimization of pharmacokinetics, multivalency and multispecificity.

Asial said that Dotbio's pipeline is focused on prevalent cancers with unmet therapeutic needs, such as liver, lung and gastric cancers, among others.

"Our candidates are validated in vitro, and the seed funding obtained will allow us to pursue preclinical validations in animal models," said Asial.

"The potential of domain antibody technology to change the way we treat cancer is clear. Our focus is on applying the world-leading protein science expertise of our team to revolutionize multispecific, CAR T and ADC therapies," he added.

> *"Multispecific domain antibodies offer a more refined means to activate the antitumor immune response and to minimize adverse effects as compared to standard antibody-based combination therapies.*
>
> Pär Nordlund
> Co-founder, Dotbio

Dotbio's current internal pipeline is focused on multispecific immuno-oncology drugs targeting different checkpoint blockades, positive immune signals and tumor-specific processes, with several candidates planned to enter preclinical studies this year. But the broad applicability of the Dotbody technology could also enable the company to consider other therapeutic areas on a case-by-case basis.

"The Dotbody technology can also be applied to many other therapeutic areas and we look forward to opportunities to collaborate with industry partners and academia to realize the enormous potential of our technology," said Nordlund.

But as a new company that has just launched, Dotbio is focusing its energy on pursuing the preclinical validation of its therapeutic candidates. The company plans to release additional information about those candidates sometime in early 2019.

As part of the spin-out agreement with NTU, Dotbio will acquire the rights to the domain antibody technology through NTUitive, the university's innovation and enterprise company. It will also obtain certain assets developed under a previous collaboration agreement between Aslan Pharmaceuticals Ltd. and NTU.

Dotbio could not offer any further comments on its plans for the assets from Aslan at this stage.

NTU and Aslan will hold minority equity stakes in Dotbio. Kingsley Leung, representing Heungkong Group, and Carl Firth, the CEO of Aslan, will join the board of Dotbio as nonexecutive directors.

Besides the capital injection, Dotbio is also laying the foundations to take its candidates to the next stage through collaborations with NTU and Sweden's Karolinska Institute and other partnerships.

"Dotbio's co-founder, Pär Nordlund, is coordinating our collaborative efforts at NTU and Karolinska Institute, with the aim of understanding better the synergistic effects of our multispecific therapeutic candidates," said Asial.

Asial said that Dotbio would be looking to raise additional funds in 2019 to complete its IND-enabling studies for the most promising drug candidates.

"We are looking at a series A round in the range of $20 million, dependent on the results obtained in 2018 and early 2019," said Asial. ♦

Financings

Acelrx Pharmaceuticals Inc., of Redwood City, Calif., said the underwriters of its public offering have exercised in full their option to purchase an additional 1.09 million shares of its common stock. That brings the total gross proceeds from the offering of 8.36 million shares at $2.75 each to approximately $23 million.

Apexigen Inc., of San Carlos, Calif., said it completed its series B and series C financings, raising a total of $73 million. A $15 million series B financing was led by Decheng Capital and a $58 million series C financing was led by 3E Bioventures Capital, Virtus Inspire Ventures and SV Tech Ventures. The company intends to use the proceeds to advance the clinical development of its lead immuno-oncology therapeutic, APX-005M, a monoclonal antibody targeting CD40. Currently, it is in multiple phase II trials to treat different types of cancers. The proceeds will also be used to discover and develop Apexigen's broader pipeline of therapies.

Dnalite Therapeutics Inc., of San Francisco, raised $1.5 million in seed financing, which will be used to continue development of gastrointestinal tract gene therapy treatments for genetic intestinal diseases using its delivery platform technology. Dnalite was founded by University of California, Berkeley graduates Mubhij Ahmad and Timothy Day in 2016. The seed round was led by Berkeley Catalyst Fund, with participation from UC Berkeley, Blue Bear Ventures, SOSV and the Baldota family, alongside Chinese biopharma **Brightgene Bio-Medical Technology Co. Ltd.** and Silicon Valley-based SVE Capital.

Edigene Inc., of Beijing, said it completed an approximately $15 million series pre-B financing led by new investor Lilly Asia Ventures. The company is headquartered in Beijing, and has operational subsidiaries in Guangzhou, China, and Cambridge, Mass. It is leveraging its platforms to develop gene-editing therapies for a wide range of diseases, and conducting high-throughput genome screening to enable dissection of functional big data in biological contexts.

GT Biopharma Inc., of Los Angeles, said it completed a private placement of convertible debentures for gross proceeds of $5.14 million. The debentures, which have a 10 percent interest rate, are convertible into the company's common stock at an initial exercise price of $2 per share, subject to adjustment. The company's most advanced oncology drug candidate, OXS-1550 (DT-2219), is a bispecific recombinant fusion protein-drug conjugate targeting CD19 and CD22 on lymphoma and leukemia cells with a modified form of diphtheria toxin as its cytotoxic drug payload. OXS-1550 has demonstrated success in early clinical trials in patients with relapsed/refractory B-cell lymphoma or leukemia.

Progenics Pharmaceuticals Inc., of New York, said it priced an underwritten public offering of 9.09 million primary shares of its common stock at $8.25 per share with gross proceeds expected to be approximately $75 million. The underwriters have been granted a 30-day option to purchase 1.36 million additional shares of common stock on the same terms and conditions. Progenics intends to use the net proceeds for research and development and general corporate purposes.

SQZ Biotechnologies Co., of Watertown, Mass., said it completed an oversubscribed $72 million series C financing round. Proceeds will support SQZ's most advanced programs in solid tumors and auto-immunity. The company's lead program in antigen presenting cells (APCs) for oncology will have its first application in multiple human papillomavirus-positive tumor indications; future applications will address solid tumors across cancer types. SQZ's APCs are engineered to deliver tumor-associated antigens that aim to prime and activate a patient's endogenous killer T cells against the target of choice in order to infiltrate tumors and destroy them.

Tot Biopharm Co. Ltd., of Suzhou, China, said it completed a series B financing round, raising $102 million. The company focuses on the R&D, manufacturing and marketing of antitumor drugs and has more than 10 drugs at the research stage, including three biologics and three small molecules, which have received IND approvals, as well as one antibody-drug conjugate, which is expected to receive approval in the near future.

Zogenix Inc., of Emeryville, Calif., said it priced an underwritten public offering of 6 million shares of its common stock at $52 each for expected gross proceeds of $312 million. The underwriters have been granted a 30-day option to purchase up to an additional 900,000 shares of common stock. The company intends to use the net proceeds to fund regulatory submissions and commercial infrastructure of ZX-008 for Dravet syndrome, to fund clinical research and development of ZX-008, including phase III development for Lennox-Gastaut syndrome, and for working capital and general corporate purposes.

Appointments and advancements

Adlai Nortye Biopharma Co. Ltd., of Hangzhou, China, appointed Lars E. Birgerson chief development officer and president and CEO of Adlai Nortye USA Inc.

Allergan plc, of Dublin, appointed Michael E. Greenberg to its board.

Alpine Immune Sciences Inc., of Seattle, appointed Mark Litton president and chief operating officer.

Alzheon Inc., of Framingham, Mass., appointed Neil Flanzraich vice chairman of its board.

Amag Pharmaceuticals Inc., of Waltham, Mass., appointed Brian Robinson senior vice president of medical affairs.

Antares Pharma Inc., of Ewing, N.J., appointed James Tursi executive vice president, head of research and development, chief medical officer.

Aobiome Therapeutics Inc., of Cambridge, Mass., appointed Klaus Dugi, Anna Lisa Jenkins and Doug Rosefsky to its board.

Athersys Inc., of Cleveland, appointed Greg Liposky senior vice president of commercial manufacturing.

Atlantic Healthcare plc, of Cambridge, U.K., appointed John Temperato U.S. president and chief operating officer.

Bellicum Pharmaceuticals Inc., of Houston, appointed Thierry Darcis general manager of Europe.

Bioxcel Therapeutics Inc., of New Haven, Conn., appointed Michael De Vivo vice president, neuroscience.

Briacell Therapeutics Corp., of Vancouver, British Columbia, appointed Shaker R. Dakhil lead principal investigator of its Bria-IMT clinical trial site and rollover studies.

Bridge Therapeutics Inc., of Birmingham, Ala., appointed Jeffrey Fudin to its scientific advisory board.

Cara Therapeutics Inc., of Stamford, Conn., appointed Christopher A. Posner to its board.

Casma Therapeutics Inc., of Cambridge, Mass., appointed Jeffrey Saunders senior vice president of drug discovery and Daniel Ory senior vice president of translational medicine.

Catalyst Pharmaceuticals Inc., of Coral Gables, Fla., appointed Jason James senior vice president of commercial operations and analytics, Jeff Del Carmen senior vice president of sales and marketing, Kevin Rohrbach senior director of patient engagement/advocacy and Maria Pandolfo senior director of patient services.

Cellectis SA, of Paris, appointed Stefan Scherer senior vice president clinical development and deputy chief medical officer.

Celyad SA, of Mont-Saint-Guibert, Belgium, appointed Filippo Petti chief financial officer, effective Sept. 3.

Cue Biopharma Inc., of Cambridge, Mass., appointed Frank Morich to its board.

Denali Therapeutics Inc., of South San Francisco, appointed Dana Andersen chief technical and manufacturing officer.

Edigene Inc., of Beijing, appointed Dong Wei CEO.

Elite Pharmaceuticals Inc., of Northvale, N.J., appointed Aqeel A. Fatmi to its board.

Endo International plc, of Dublin, appointed Laure Park senior vice president, investor relations and corporate affairs.

Eyegate Pharmaceuticals Inc., of Waltham, Mass., appointed Peter Greenleaf to its board.

Gamida Cell Ltd., of Jerusalem, appointed Jaren Madden vice president, investor relations and corporate communications.

Immune Therapeutics Inc., of Orlando, Fla., appointed Roscoe Moore Jr. chair of its board and to its scientific advisory board.

Infinity Pharmaceuticals Inc., of Cambridge, Mass., appointed Samuel Agresta chief medical officer.

Lixte Biotechnology Holdings Inc., of East Setauket, N.Y., appointed Yun Yen and Winson (Sze Chun) Ho to its board.

Mabvax Therapeutics Holdings Inc., of San Diego, appointed Gregory Hanson to its board.

Marina Biotech Inc., of City of Industry, Calif., appointed Jay D. Schwartz senior vice president, commercial operations.

Merck & Co. Inc., of Kenilworth, N.J., appointed Steven C. Mizell chief human resources officer, effective in October.

Navitor Pharmaceuticals Inc., of Cambridge, Mass., appointed Thomas E. Hughes CEO; George P. Vlasuk will remain president and was appointed chief scientific officer.

Neuralstem Inc., of Germantown, Md., appointed Jim Scully interim CEO and William Oldaker chair of its board.

Novocure Ltd., of St. Helier, Jersey, elected Jeryl Hilleman to its board.

Omeros Corp., of Seattle, appointed Eckhard Leifke chief medical officer and vice president of clinical development.

Oncobiologics Inc., of Cranbury, N.J., appointed Lawrence A. Kenyon president and CEO and to its board.

Orchard Therapeutics Ltd., of London, appointed Jon Ellis to its board.

Rallybio LLC, of Farmington, Conn., appointed Laura Ekas and Eric Watsky to its executive team.

Rockwell Medical Inc., of Wixom, Mich., appointed Stuart Paul CEO, effective Sept. 4.

Sienna Biopharmaceuticals Inc., of Westlake Village, Calif., appointed James M. Hindman to its board.

Urogen Pharma Ltd., of Ra'anana, Israel, appointed Peter P. Pfreundschuh chief financial officer, effective Aug. 20.

Vivus Inc., of Campbell, Calif., appointed Ken Suh president.

Ziopharm Oncology Inc., of Boston, elected Scott Tarriff lead director of its board.

Clinical data for Aug. 8, 2018

Company	Product	Description	Indication	Status
Phase I				
CBT Pharmaceuticals Inc., of Pleasanton, Calif.	CBT-101	Inhibitor of c-Met receptor	Locally advanced or metastatic hepatocellular carcinoma or renal cell carcinoma	Received ethics approval from the Bellberry Human Research Ethics Committee in Australia for APOLLO-1, an open-label dose-escalation and expansion study testing CBT-101 in combination with anti-PD-1 drugs CBT-501 in hepatocellular carcinoma or Opdivo (nivolumab, Bristol-Myers Squibb Co.) in renal cell carcinoma
Eurocine Vaccines AB, of Stockholm	Immunose Flu	Quadrivalent influenza vaccine	Influenza prophylaxis	In the 298-patient trial of older adults ages 50-75, the vaccine had good safety and tolerability; immunological results expected in October 2018
Oncopep Inc., of Boston	PVX-410	Tumor-associated antigens	Smoldering multiple myeloma	Started the 20-patient safety and tolerability study testing VX-410 in combination with HDAC 6 inhibitor citarinostat (CC-96241, Celgene Corp.) or in combination with citarinostat and lenalidomide
Regenxbio Inc., of Rockville, Md.	RGX-314	NAV AAV8 vector encoding a VEGF-inhibiting antibody fragment	Wet age-related macular degeneration	The 6 patients in cohort 3, who received the highest dose tested, had the highest level of protein expression, declines in central retinal thickness of 21 µm and increased in best corrected visual acuity of 8 Early Treatment Diabetic Retinopathy Study letters; through 6 months, 50% of patients were free of anti-VEGF intravitreal injections; expanding trial to a fourth dose of 1.6 x 10^11 GC/eye with the first patient in that cohort already treated
Regenxbio Inc., of Rockville, Md.	RGX-501	NAV AAV8 vector encoding the LDLR gene	Homozygous familial hypercholest-erolemia	All 3 patients in cohort 2 had elevation in transaminases, which was lowered with treatment of prednisone; plans to amend protocol to include steroid prophylaxis at dose for cohort 2 before advancing to cohort 3
Phase II				
Bavarian Nordic A/S, of Copenhagen, Denmark	MVA-BN RSV	Respiratory syncytial virus vaccine	Respiratory syncytial virus prophylaxis	In an 88-patient extension study, testing a booster shot of the vaccine, the broad antibody responses against RSV were durable and remained elevated compared to baseline in at least 60% of patients 1 year after receiving the booster
Ra Pharmaceuticals Inc., of Cambridge, Mass.	RA-101495 SC	Complement component 5 inhibitor	Generalized myasthenia gravis	Completed enrollment of the 44-patient placebo-controlled study; top-line data expected around year-end 2018
Phase III				
Clovis Oncology Inc., of Boulder, Colo.	Rubraca (rucaparib)	PARP inhibitor	Advanced ovarian cancer	Enrolled first of approximately 1,000 patients in the Athena study testing Rubraca plus Opdivo (nivolumab, Bristol-Myers Squibb Co.) as a maintenance treatment; investigator-assessed progression-free survival will be measured as the primary endpoint; secondary endpoints include overall survival, objective response rate, duration of response and safety
Biondvax Pharmaceuticals Ltd., of Ness Ziona, Israel	M-001	Universal influenza vaccine	Influenza prophylaxis	Enrolled first of 9,630 participants in study measuring protection from influenza and safety of M-001 as the primary endpoints; reduction in flu illness severity will be measured as a secondary endpoint
Milestone Pharmaceuticals Inc., of Montreal	Etripamil	Short-acting calcium channel blocker	Paroxysmal supraventricular tachycardia	Enrolled first of up to 500 patients in the placebo-controlled study measuring the time to conversion of the sporadic heart arrhythmia to sinus rhythm after administration of the drug; secondary endpoints include relief of symptoms commonly associated with an arrhythmia episode, such as heart palpitations, chest pain, anxiety, shortness of breath, dizziness and fainting
Pluristem Therapeutics Inc., of Haifa, Israel	PLX-PAD	Placental-derived adherent stromal cells	Critical limb ischemia	Israel's Ministry of Health cleared the start of patient recruitment in Israel in the ongoing 246-patient study that is currently recruiting patients in the U.S., U.K., Germany, Poland, Czech Republic, Hungary, Bulgaria and Macedonia
Pluristem Therapeutics Inc., of Haifa, Israel	PLX-PAD	Placental-derived adherent stromal cells	Muscle injury following hip fracture surgery	Israel's Ministry of Health cleared the start of patient recruitment in Israel in the ongoing 240-patient study

Company	Product	Description	Indication	Status
Strongbridge Biopharma plc, of Dublin	Recorlev (levoketocon-azole)	Cortisol synthesis inhibitor	Cushing's syndrome	The Sonics study met its primary endpoint with 30% of patients achieving normalization of mean urinary free cortisol after 6 months of treatment; fasting blood glucose, hemoglobin A1C, total cholesterol, low-density lipoprotein-cholesterol, body weight and body mass index all improved from baseline (p<.0001 for each)
United Therapeutics Corp., of Silver Spring, Md.	Orenitram (treprostinil)	Prostacyclin vasodilator	Pulmonary arterial hypertension	In the 690-patient Freedom-Ev study, Orenitram reduced the risk of a morbidity/mortality event compared to placebo by 26% (p=0.0391); company plans to submit data to FDA to expand label

Notes

For more information about individual companies and/or products, see Cortellis.

Regulatory actions for Aug. 8, 2018

Company	Product	Description	Indication	Status
Alector Inc., of South San Francisco	AL-001	Human recombinant monoclonal antibody designed to increase progranulin levels	Frontotemporal dementia	FDA granted orphan designation
Ampio Pharmaceuticals Inc., of Englewood, Colo.	Ampion	Low-molecular-weight fraction of 5% human serum albumin	Pain due to osteoarthritis of the knee	Company disclosed in an SEC filing that in response to a meeting with the FDA in July, the agency said the AP-003-A trial alone does not appear to provide sufficient evidence to support a BLA and recommended the firm perform an additional randomized trial under a special protocol assessment; Ampio said it will continue discussions with the FDA; company shares (NASDAQ:AMPE) fell 79% Wednesday to close at 61 cents
Genmab A/S, of Copenhagen, Denmark, and Janssen Biotech Inc., a unit of Johnson & Johnson, of New Brunswick, N.J.	Darzalex (daratumum-ab)	Human IgG1k monoclonal antibody binding to CD38	Multiple myeloma	Submitted a supplemental BLA to the FDA and a type II variation to the EMA seeking approval of a split dosing regimen, offering the option of splitting the first infusion over 2 consecutive days; applications are supported by data from the phase Ib EQUULEUS trial
Glenmark Pharmaceuticals Ltd., of Mumbai, India	Ryaltris (olopatadine hydrochloride/ mometasone furoate, GSP-301)	Fixed-dose combo of antihistamine and steroid in nasal spray	Seasonal allergic rhinitis	FDA accepted for review NDA seeking approval for use in patients 12 and older; Ryaltris conditionally accepted by FDA as brand name
Kyowa Hakko Kirin Co. Ltd., of Tokyo	Poteligeo (mogamuli-zumab-kpkc)	CCR4-targeting monoclonal antibody	Relapsed or refractory mycosis fungoides and Sezary syndrome	Approved by FDA under priority review
Morphosys AG, of Martinsried, Germany, and I-Mab Biopharma Co. Ltd., of Shanghai	TJ-202/MOR-202	Human monoclonal antibody directed against CD38	Multiple myeloma	Submitted an IND to the China National Drug Administration
Vertex Pharmaceuticals Inc., of Boston	Orkambi (lumacaftor/ ivacaftor)	CFTR corrector/ CFTR potentiator	Cystic fibrosis	Approved by FDA to include use in children, ages 2 through 5, with CF who have 2 copies of the F508del-CFTR mutation

Notes

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